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# DERIVATIVE OF BIOACTIVE SUBSTANCE K-252

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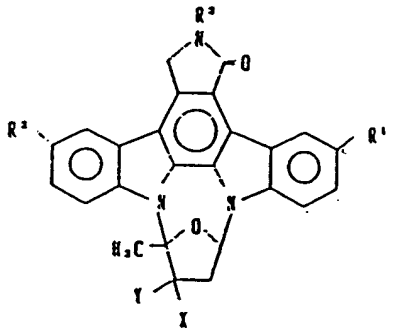
[Attached amendments have been incorporated into text of translation.]

Claim

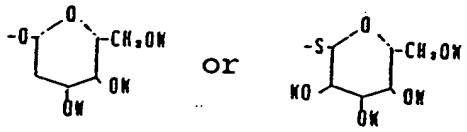
A type of K-252 derivative represented by the following formula, and its pharmacologically tolerable salts:



(where $R^1$ and $R^2$, which may be identical or different from each other, represent hydrogen, methyl, hydroxymethyl, lower alkoxymethyl, lower alkylthiomethyl, lower alkylsulfinylmethyl, nitro, bromo, lower alkanoyl, hydroxy, lower alkanoyloxy, lower

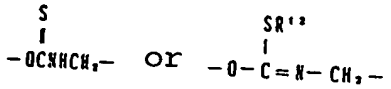
alkoxy, $-NR^4R^5$ (where one of $R^4$ and $R^5$ represents hydrogen and the other represents hydrogen, lower alkanoyl, carbamoyl, lower alkylaminocarbonyl or phenylaminocarbonyl, or both may represent lower alkyl), sulfonic acid, $-SO_2NR^6R^7$ (where $R^6$ and $R^7$, which may be identical or different from each other, represent hydrogen, lower alkyl or groups that form a heterocycle with the adjacent nitrogen atoms), $-OCOOR^8$ (where $R^8$ represents lower alkyl or substituted or unsubstituted phenyl) or $-OCONR^6R^7$ (where $R^6$ and $R^7$ have the same definitions as above); $R^3$ represents hydrogen, chlorine, lower alkanoyl, carbamoyl or lower alkyl; X represents hydroxymethyl, formyl, carboxyl, lower alkoxycarbonyl, lower alkylhydrazinocarbonyl, $-CH=N-R^9$ (where $R^9$ represents hydroxy, carbamoylamino, $-NR^6R^7$ (where $R^6$ and $R^7$ have the same definitions as above), guanidino, or 2-imidazolylamino), $-CONHR^{10}$ (where $R^{10}$ represents the residue of an α-amino acid after its amino group is removed; the carboxyl group of the amino acid may be esterified by lower alkyl or benzyl), $-CH_2OCR^{11}$ (where $R^{11}$ represents the residue of an α-amino acid after its carboxyl group is removed; the amino group of the amino acid may be protected by benzyloxycarbonyl or t-butoxycarbonyl), or $-CH_2Z$ (where Z represents a sugar residue represented by

JP text says $CH_2OCR^{11}$



(where W represents hydrogen, methyl, ethyl, benzyl, acetyl or trifluoroacetyl)); Y represents hydroxy, lower alkanoyloxy,

carbamoyloxy or a lower alkoxy group; also, X and Y may be combined to form -Y-X-, which may be $-O-C(CH_3)_2-O-CH_2-$,



(where $R^{12}$ represents lower alkyl);

when X represents hydroxymethyl, carboxyl or lower alkoxycarbonyl, among $R^1$, $R^2$ and $R^3$, at least one represents a group other than hydrogen; when $R^1$ and $R^2$ represent hydrogen and $R^3$ represents acetyl, X cannot represent methoxycarbonyl at the same time Y represents acetoxy).

Detailed explanation of the invention

Industrial application field

This invention concerns a novel compound that can inhibit protein kinase C (referred to as C-kinase hereinafter), and has various pharmacological effects.

Prior art

C-kinase is a type of protein-phosphorylating enzyme, which is activated by phospholipid and calcium, and is widely distributed in biological tissues and internal organs. Recently, it has been found that this type of enzyme has a very important role in the cell membrane receiving/transmission mechanism of many types of hormones and neurotransmitting substances. There

are reports on the following examples of the physiological reactions caused by the information transmission mechanism related to C-kinase: in platelets, release of serotonin, liberation of lysosomal enzymes and the coagulation reaction; in neutrophils, formation of superoxides and liberation of lysosomal enzymes; liberation of epinephrine from the suprarenal medulla, secretion of aldosterone from the glomerulus, secretion of insulin from Langerhans' cells, liberation of histamine from mastocytes, liberation of acetylcholine from the ileum, smooth muscle contraction in blood vessels, etc. Also, C-kinase is believed to be related to the mechanism of cell reproduction and cancer induction (see: Y. Nishizuka, Science, 225, 1365 (1984); H. Rasmussen ea al., Advance in Cyclic Nucleotide and Protein Phosphorylation Research, Vol. 18, P159, edited by P. Greengard and G. A. Robison, Raven Press, New York, 1984).

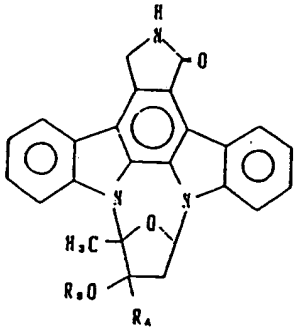
In this way, it is clear that C-kinase is related to many important physiological reactions and various conditions of disease in the organisms. Consequently, it is believed that if the C-kinase activity can be controlled by using specific suppressants, it might be possible to prevent and treat various circulatory diseases, as well as inflammation, allergy, tumors, etc.

On the other hand, it has been found that trifluoperazine, chlorpromazine and other drugs for treating psychosis, Dibenamine and tetracaine and other local narcotics, calmodulin suppressant W-7 (N-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide), and

other drugs can inhibit C-kinase. However, for all of these drugs, the C-kinase-inhibiting effect is not the principal effect of the drugs, the specificity is low, and the inhibiting activity is also low. (see:

[Y. Nishizuka et al., J. Biol. Chem., 255, 8378 (1980); R. C. Schatzman et al., Biochem. Biophys. Res. Commun., 98, 669 (1981); B. C. Wise et al., J. Biol. Chem., 257, 8489 (1982)].

On the other hand, there are K-252, KT-5556 and derivatives of K-252 with the $R_A$ and $R_B$ portions modified (for K-252, see Japanese Kokai Patent Application No. Sho 60[1985]-41489 and U.S. Patent No. 455,402; for KT-5556, see Japanese Kokai Patent Application No. Sho 61[1986]-176531; for derivatives of K-252, see Japanese Kokai Patent Application Nos. Sho 62[1987]-155284 and Sho 62[1987]-155285).



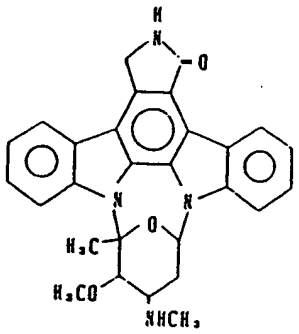
K-252: $R_A = CO_2CH_3$, $R_B = H$

KT-5556: $R_A = CO_2H$, $R_B = H$

It is described in Japanese Kokai Patent Application No. Sho 60[1985]-41489 that K-252 is effective in inhibiting the

liberation of histamine and has an antiallergic effect. In Japanese Kokai Patent Application Nos. Sho 62[1987]-155284 and Sho 62[1987]-155285, it is described that the K-252 derivative has C-kinase inhibiting activity and inhibits the liberation of histamine. On the other hand, it is described in Japanese Kokai Patent Application No. Sho 61[1986]-176531 that KT-5556 inhibits the liberation of histamine. In another report (M. Senzaki et al., J, Antibiotics, Vol. 38, p. 1437 (1985)). It was reported that a compound estimated to be of the same type of compound as K-252 and KT-5556 displayed an antibiotic effect. Also disclosed in this reference are compounds with $R_A$ = $CO_2CH_3$ and $R_B$ = $COCH_3$. Japanese Kokai Patent Application Nos. Sho 62[1987]-120388 and Sho 62[1987]-164628 disclosed a type of compound believed to be identical to K-252 and its halogen derivatives. In Japanese Kokai Patent Application No. Sho 62[1987]-240689, a derivative with $R_A$ modified was disclosed. All of these compounds decrease blood pressure and have the diuretic effect.

Also, there is a substance known as staurosporine, which has the structure shown below, similar to that of K-252, and which has antibiotic function (S. Omura et al., J. Antibiotics, Vol. 30, p. 275 (1977); A. Furusaki et al., J. Chem. Soc. Chem. Commun., p. 800 (1978)); Japanese Kokai Patent Application No. Sho 60[1985]-185719).



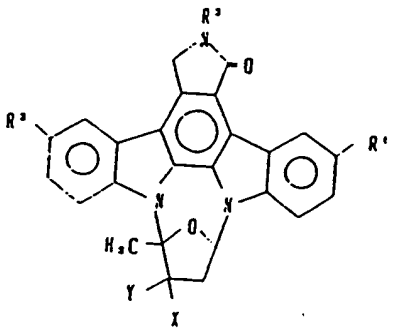

Staurosporine

Problems to be solved by the invention

There is always a demand for the development of new active components with high C-kinase-inhibiting activity for use as antiallergic agents, antithrombotic agents, anti-inflammation agents, and antineoplastic agent.

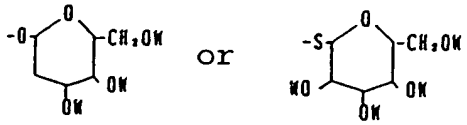
Means to solve the problems

This invention provides a type of K-252 derivative represented by the following formula (I), and its pharmacologically tolerable salts:

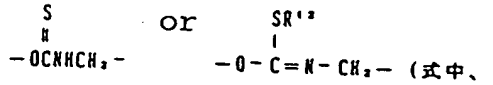



(I)

(where $R^1$ and $R^2$, which may be identical or different from each other, represent hydrogen, methyl, hydroxymethyl, lower alkoxymethyl, lower alkylthiomethyl, lower alkylsulfinylmethyl, nitro, bromo, lower alkanoyl, hydroxy, lower alkanoyloxy, lower alkoxy, $-NR^4R^5$ (where one of $R^4$ and $R^5$ represents hydrogen and the other represents hydrogen, lower alkanoyl, carbamoyl, lower alkylaminocarbonyl or phenylaminocarbonyl or both may represent lower alkyl), sulfonic acid, $-SO_2NR^6R^7$ (where $R^6$ and $R^7$, which may be identical or different from each other, represent hydrogen, lower alkyl or groups that form a heterocycle with the adjacent nitrogen atoms), $-OCOOR^8$ (where $R^8$ represents lower alkyl or substituted or unsubstituted phenyl) or $-OCONR^6R^7$ (where $R^6$ and $R^7$ have the same definitions as above); $R^3$ represents hydrogen, chlorine, lower alkanoyl, carbamoyl or lower alkyl; X represents hydroxymethyl, formyl, carboxyl, lower alkoxycarbonyl, lower alkylhydrazinocarbonyl, $-CH=N-R^9$ (where $R^9$ represents hydroxy, carbamoylamino, $-NR^6R^7$ (where $R^6$ and $R^7$ have the same definitions as above), guanidino, or 2-imidazolylamino), $-CONHR^{10}$ (where $R^{10}$ represents the residue of an α-amino acid after its amino group is removed; the carboxyl group of the amino acid may be esterified by lower alkyl or benzyl), $-CH_2OCR^{11}$ (where $R^{11}$ represents the residue of an α-amino acid after its carboxyl group is removed; the amino group of the amino acid may be protected by benzyloxycarbonyl or t-butoxycarbonyl), or $-CH_2Z$ (where Z represents a sugar residue represented by



(where W represents hydrogen, methyl, ethyl, benzyl, acetyl or trifluoroacetyl); Y represents hydroxy, lower alkanoyloxy, carbamoyloxy or a lower alkoxy group; also, X and Y may be combined to form -Y-X-, which may be $-O-C(CH_3)_2-O-CH_2-$



(where $R^{12}$ represents lower alkyl);

when X represents hydroxymethyl, carboxyl or lower alkoxycarbonyl, among $R^1$, $R^2$ and $R^3$, at least one represents a group other than hydrogen; when $R^1$ and $R^2$ represent hydrogen and $R^3$ represents acetyl, X cannot represent methoxycarbonyl at the same time Y represents acetoxy).

In the following, the compound represented by formula (I) will be referred to as compound (I). The same rule applies for the other numbered compounds. Compound (I) has not only on excellent C-kinase inhibiting activity, but also an excellent inhibiting effect in preventing the liberation of histamine, preventing the coagulation of blood platelets, preventing inflammation and inhibiting the growth of cells.

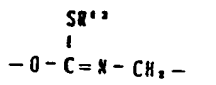
In the definitions of the various groups in formula (I), the lower alkyls referred to in the lower alkoxymethyl, lower alkylthiomethyl, lower alkoxy, lower alkylaminocarbonyl, lower alkyl, lower alkoxycarbonyl and lower alkyl hydrazinocarbonyl include C1-4 linear and branched alkyls, such as methyl, ethyl, n-propyl, i-propyl, t-butyl, n-butyl, etc. In the definitions of the various groups, the lower alkanoyls referred to in the lower alkanoyl and lower alkanoyloxy include $C_{1-4}$ linear and branched

alkanoyls, such as formyl, acetyl, propionyl, n-butyryl, i-butyryl, etc. In the definitions of the various groups, examples of the heterocycles formed include pyrrolidine, piperidine, N-substituted piperazine, morpholine, N-substituted homopiperazine, etc. Examples of the substituents include methyl, ethyl and other lower alkyls, as well as i-propylaminocarbonylmethyl, etc.

In the definition of $R^8$ examples of the substituents of the substituted phenyl include lower alkyl, lower alkoxy, nitro, halogen, etc. In this case, the types of lower alkyl and lower alkoxy are identical to those listed above, and examples of halogen include fluorine, chlorine, bromine and iodine.

In the definitions of $R^{10}$ and $R^{11}$, examples of $\alpha$-amino acids include glycine, alanine, valine, proline, etc. They may be L-, D- or racemic materials. The types of the lower alkyls referred to in the lower alkyl esters of the amino acids also include the aforementioned types.

When compound (I) is an acidic compound, it is possible to form its base addition salt, and when it is a basic compound, it is possible to form an acid addition salt. In this case, the acidity is realized by means of carboxy, etc., when X includes an $\alpha$-amino acid residue; the basicity is realized by means of amino in $R^1$, $-CH=N-R^3$ (except when $R^3$ = OH) in (di-) lower alkylamino and X, and, when an $\alpha$-amino acid group is contained,



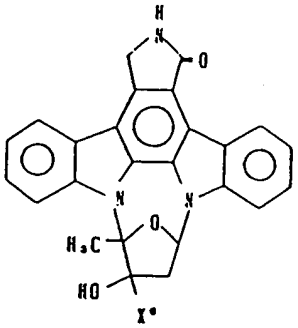
in amino-Y-X-, etc. Examples of the base addition salts of compound (I) include the ammonium salt, lithium salt, sodium salt, potassium salt and other alkali

metal salts, calcium salt, magnesium salt and other alkaline-earth salts, salts of triethylamine, morpholine, piperidine, dicyclohexylamine and salts of other organic bases, salts of arginine, lysine and salts of other basic amino acids, etc. Examples of the acid addition salts of compound (I) include the hydrochloride salt, hydrobromide salt, sulfate salt, nitrate salt, formate salt, acetate salt, benzoate salt, maleate salt, fumarate salt, succinate salt, tartrate salt, citrate salt, oxalate salt, methanesulfonate salt, toluenesulfonate salt, aspartate salt, glutamate salt, etc. The nontoxic and pharmacologically tolerable salts, such as the aforementioned base addition salts and acid addition salts, are preferred. However, other salts are also useful for isolation and refinement.

The compound in this invention is prepared in a conventional stereospecific reaction from optically active K-252. Also, all of the possible sterioisomers and their mixtures are also included in this invention.

In the following, the manufacturing method of compound (I) in this invention will be explained. However, the manufacturing method of compound (I) is not limited to the method explained in the following.

Compound (I) may be prepared using various preparation methods from K-252 and the compounds represented by following formulas (IIa and b) derived from it:



(II)

(IIa) ($X^a$ = COOH)

(IIb) ($X^a$ = $CH_2OH$)

Compound (IIa) is disclosed in Japanese Kokai Patent Application No. Sho 61[1986]-176531, and compound (IIb) is disclosed in Japanese Kokai Patent Application No. Sho 62[1987]-155285 (see Reference Example 5).

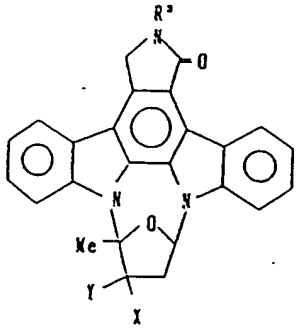
In the manufacturing method to be presented in the following, when the defined groups vary under the conditions of the implementation method or when the method is inappropriate for implementation, the conventional methods often used in organic synthetic chemistry, such as the protection and deprotection of functional groups, or other means (for example, see: Green: "Protective groups in organic synthesis," published by John Wiley and Sons, Inc. (1981)) can be adopted easily (for example, see Application Example 2).

In the formulas, tables, etc., to be presented below, the symbols Me, Et, Pr, Bu, Ph, Ac, Bzl, Cbz, and Ts stand for

methyl, ethyl, propyl, butyl, phenyl, acetyl, benzyl, benzyloxycarbonyl and toluenesulfonyl groups, respectively.

Method 1. Synthesis of compound (I-1) with functional groups in $R^1$ and/or $R^2$

1-1. Compound (I-1-1) and/or (I-1-1') with $R^1$ and/or $R^2$ representing nitro



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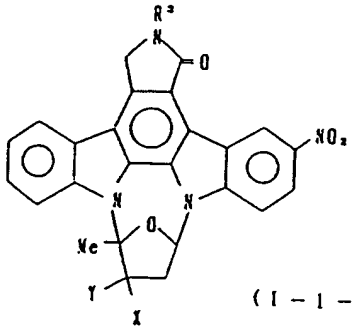
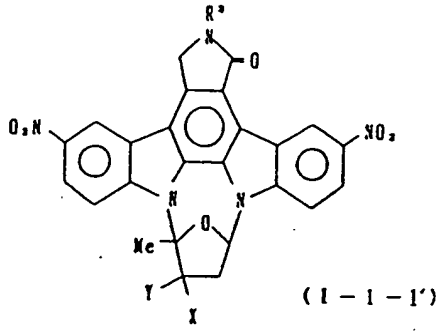


(I-1-1)

Key: 1 Nitration



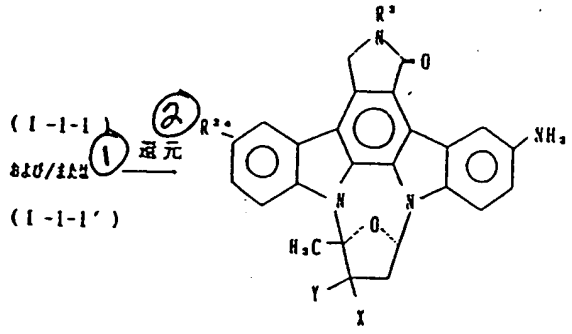
(I-1-1')

(where X, Y, and $R^3$ have the same meanings as above).

Compounds (I-1-1) and/or (I-1-1') can be obtained in a reaction between compound (III-1) (compound with $R^1$ and $R^2$ representing hydrogen in compound (I), and compound (II)) and an appropriate nitrating agent, such as nitronium tetrafluoroborate, in a medium inert to the reaction. The amount of the nitrating agent is usually in the range of 1-1.1 Eq with respect to compound (III-1). Examples of the inert solvents include sulfolane, acetonitrile, chloroform, etc. The reaction is carried out at a temperature in the range of room temperature to 80°C and is usually carried out for 1-2 h.

1-2. Compound (I-1-2) with $R^1$ and/or $R^2$ represent $-NR^4R^5$

1-2a. Compound (I-1-2a) and/or (I-1-2a′) with $R^4$ and $R^5$ representing hydrogen




(I-1-2a) ($R^{2a}$=H)

(I-1-2a′) ($R^{2a}$=$NH_2$)

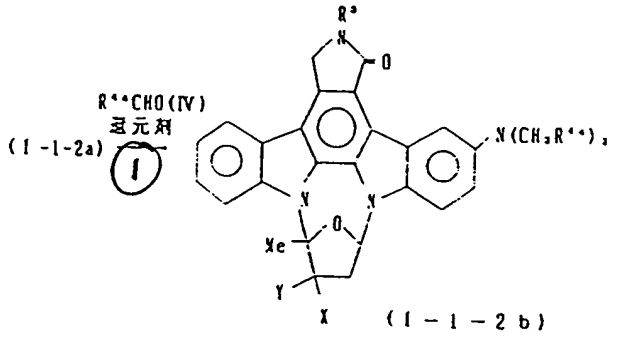
Key: 1 And/or
2 Reduction

(where X, Y, and $R^3$ have the same meanings as above, and $R^{2a}$ represents hydrogen or amino).

Compounds (I-1-2a) and/or (I-1-2a′) are prepared by means of reduction using an appropriate reduction method, such as catalytic reduction on the nitro substances (I-1-1) and/or (I-1-1′). The type of catalyst includes 5-10% palladium/carbon, etc., in an amount in the range of 0.1-0.5 times the weight of compound (I-1-1a). Examples of the inert solvents include tetrahydrofuran (THF), dimethylformamide (DMF), etc. The reaction is usually carried out at room temperature for 1 h to 1 day.

In the description of method 1 in the following, although there are cases in which there is no special description for the manufacturing method of the 2-substituted substance ($R^1 = R^2 \neq H$), the same conditions as those in the manufacturing method of the aforementioned 1-substituted substance can be applied.

1-2b. Compound I-1-2b with $R^4$ and $R^5$ representing alkyl



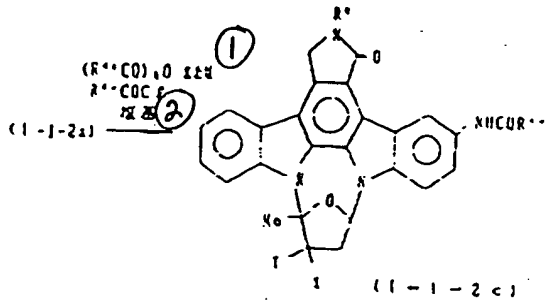

Key: 1 Reducing agent

(where X, Y and $R^3$ have the same meanings as above, and $R^{4a}$ represents hydrogen or lower alkyl).

Compound (I-1-2b) is obtained in a reaction of the amine (I-1-2a) and the aldehyde (IV) with an appropriate reducing agent, such as sodium cyanoborohydride, in an inert solvent. Usually, the amount of compound (IV) is present in significant excess with respect to compound (I-1-2a), and the amount of the reducing agent is 1-2 Eq. The inert solvent used is prepared as

a 1:1 solvent mixture of THF and an appropriate alkanol, such as methanol. The reaction is usually carried out at room temperature for 0.5-1 h.

1-2c. Compound (I-1-2c) with $R^4$ (or $R^5$ representing alkanoyl

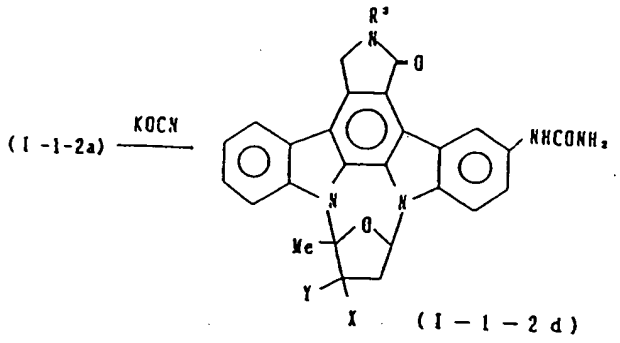


Key: 1 Or
2 Base

(where X, Y, $R^3$ and $R^{4a}$ have the same meanings as above).

Compound (I-1-2c) is manufactured in a reaction between amine (I-1-2a) and an acylating agent ($(R^{4a}CO)_2O$ or $R^{4a}COCL$, etc.) in the presence of a base. Examples of the bases that can be used include pyridine, triethylamine, etc. The amount of the acylating agent used is usually in the range of 5-10 Eq with respect to compound (I-1-2a). The reaction is usually carried out using pyridine as a solvent at room temperature for 1-6 h.

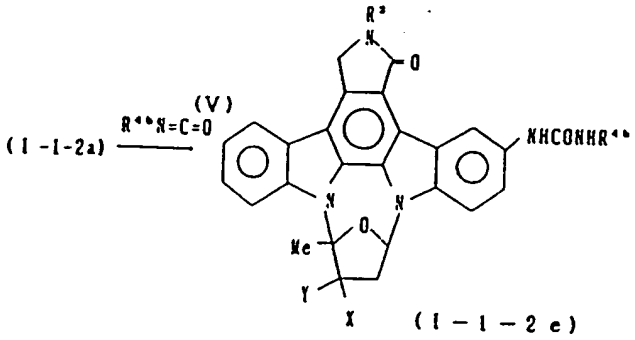
1-2d. Compound (I-1-2d) with $R^4$ (or $R^5$ representing carbamoyl




(where X, Y and $R^3$ have the same meanings as above).

Compound (I-1-2d) is prepared in a reaction between amine (I-1-2a) and potassium cyanate, in an amount of about 5 Eq in a solvent mixture of THF, acetic acid and water (10:1:1). The reaction is usually carried out at room temperature for about 1 h.

1-2e. Compound (I-1-2e) with $R^4$ (or $R^5$) representing alkylaminocarbonyl or phenylaminocarbonyl

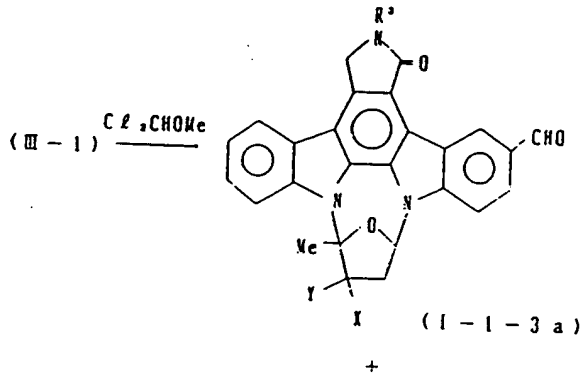


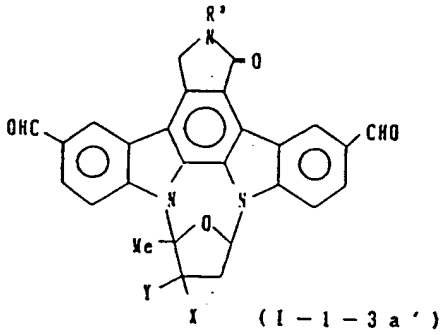
(where X, Y and $R^3$ have the same meanings as above, and $R^{4b}$ represents lower alkyl or phenyl).

Compound (I-1-2e) is obtained in a reaction between amine (I-1-2a) and isocyanate (V) in an inert solvent, and, if necessary, in the presence of a base. Examples of the bases that can be used include triethylamine, etc. With respect to compound (I-1-2a), the amount of compound (V) is usually in the range of 2-3 Eq, and the amount of the base used is in the range of 1-2 Eq. Examples of the inert solvents that can be used include dichloromethane, chloroform, etc. The reaction is usually carried out at room temperature for 1-5 h.

1-3. Compound (I-1-3) with $R^1$ and/or $R^2$ representing alkanoyl

1-3a. Compound (I-1-3a) and/or (I-1-3a') with formyl used as the alkanoyl



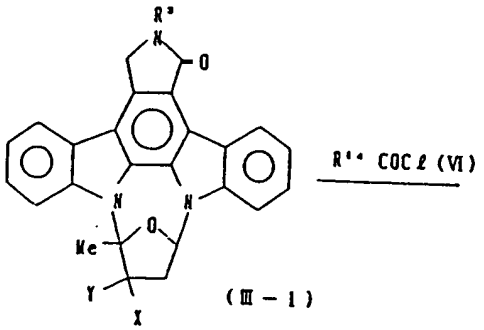



(I-1-3a')

(where X, Y and $R^3$ have the same meanings as above).

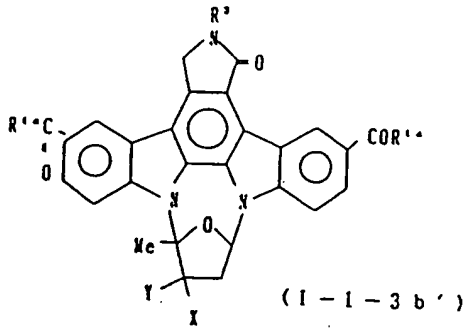
Compound (I-1-3a) and/or (I-1-3a') is formed in a reaction between compound (III-1) and dichloromethyl methyl ether in an inert solvent containing an appropriate Lewis acid, such as titanium tetrachloride. With respect to compound (III-1), the amount of dichloromethyl methyl ether used is usually in the range of 1-2 Eq, and the amount of titanium tetrachloride is usually in the range of 5-7 Eq. Dichloromethane is usually used as the inert solvent. The reaction is carried out at room temperature for 1-12 h.

1-3b. Compound (I-1-3b) and/or (I-1-3b′) with alkanoyl of a type other than formyl

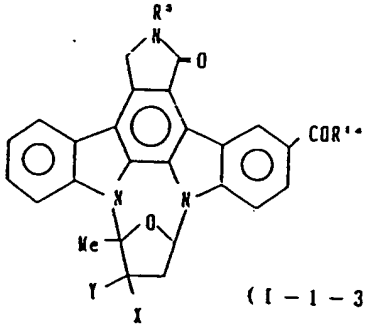



R'⁴ COCℓ (VI)

(Ⅲ－1)




(I－1－3b′)

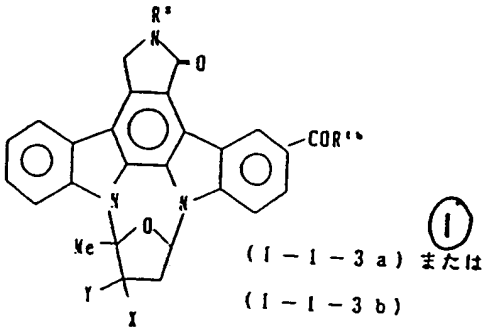



(I－1－3b)

(where X, Y, and $R^3$ have the same meanings as above, and $R^{1a}$ represents alkyl).

Compounds (I-1-3b) and/or (I-1-3b') are formed in a reaction between compound (III-1) and acid chloride (VI) in an inert solvent containing an appropriate Lewis acid, such as aluminum chloride. With respect to compound (III-1), the amount of compound (VI-1) used is usually in the range of 1 Eq, and the amount of aluminum chloride is usually 5 Eq. Dichloromethane, chloroform, etc., is usually used as the inert solvent. The reaction is carried out under ice cooling for 1-12 h.

1-4. Compound (I-1-4) with $R^1$ and/or $R^2$ representing alkanoyloxy




(I-1-4)

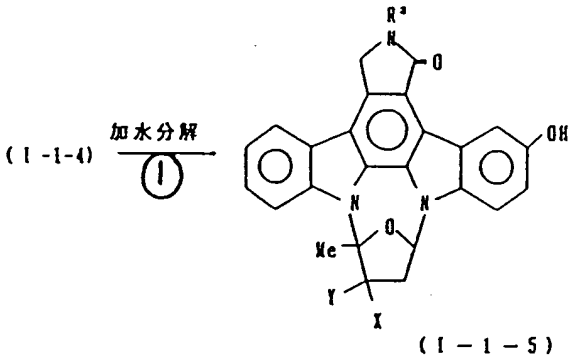
Key: 1 Or
2 m-Chloroperbenzoic acid

(where X, Y and $R^3$ have the same meanings as above, and $R^{1b}$ represents hydrogen or lower alkyl).

Compound (I-1-4) is formed in a reaction between alkanoyl substance (I-1-3a) or (I-1-3b) and an appropriate type of oxidizing agent, such as m-chloroperbenzoic acid, in an inert solvent, such as chloroform. With respect to compound (I-1-3a) or (I-1-3b), the amount of the oxidizing agent used is usually 5 Eq, and it is used twice in 1 h. The reaction is usually carried out with heating under reflux for 2-12 h.

Corresponding to the aforementioned reaction formula, it is also possible to form the 2-substituted alkanoyloxy substance (I-1-4') from the 2-substituted alkanoyl substance (I-1-3a') or (I-1-3b') under the same conditions.

1-5. Compound (I-1-5) with $R^1$ and/or $R^2$ representing hydroxy




(I-1-5)

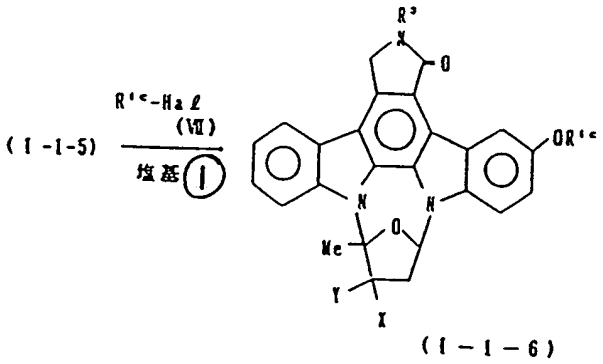
Key: 1 Hydrolysis

(where X, Y and $R^3$ have the same meanings as above).

Compound (I-1-5) is formed by the alkaline hydrolysis of alkanoyloxy substances (I-1-4). The reaction between compound (I-1-4) and sodium methylate, sodium ethylate or another sodium lower alkoxide is carried out in an inert solvent. The amount of the base with respect to compound (I-1-4) is usually in the range of 5-7 Eq. Examples of the inert solvents that can be used include dichloromethane, THF, etc. The reaction is carried out at a temperature in the range of 0°C to room temperature for 3-30 min.

Also, the corresponding 2-substituted hydroxy substance (I-1-5′) can be formed from the 2-substituted alkanoyloxy substance (I-1-4′) under the same conditions.

1-6. Compound (I-1-6) with $R^1$ and/or $R^2$ representing alkoxy




Key: 1 Base

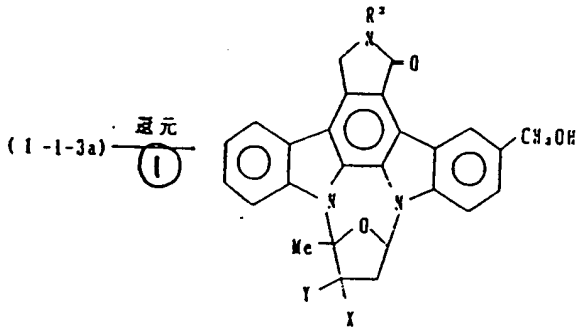
(where X, Y and $R^3$ have the same meanings as above, $R^{1c}$ represents lower alkyl, and Hal represents a halogen atom).

Compound (I-1-6) is formed in a reaction between hydroxy substance (I-1-5) and a lower alkyl halide (VII) in an inert

solvent containing base. For the lower alkyl halide, the iodide and bromide are preferred, as they have high reactivity. Examples of the bases that can be used include sodium halide, potassium t-butoxide, etc. With respect to compound (I-1-5), the amount of compound (VII) and base is usually 1 Eq. Examples of the inert solvents include DMF and THF. The reaction is usually carried out at a temperature in the range of 0°C to room temperature, for 20 min to 1 h.

Also, the corresponding 2-substituted alkoxy substance (I-1-6′) can be formed from 2-substituted hydroxy substances (I-1-5′) under the same conditions.

1-7. Compound (I-1-7) with $R^1$ and/or $R^2$ representing hydroxymethyl



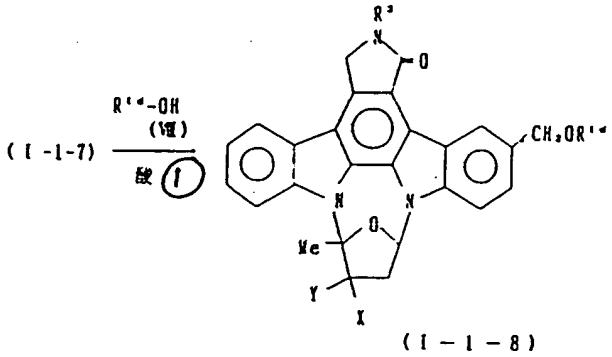

Key: 1 Reduction

(where X, Y and $R^3$ have the same meanings as above).

Compound (I-1-7) is formed in a reaction between aldehyde (I-1-3a) and an appropriate reducing agent, such as sodium borohydride, in an inert solvent. With respect to compound

(I-1-3a), the amount of the reducing agent used is usually in the range of 2-3 Eq. The inert solvent used in this case is usually a 1:1 solvent of chloroform and methanol. The reaction is usually carried out under ice cooling for 0.5-1 h.

1-8. Compound (I-1-8) with $R^1$ and/or $R^2$ representing alkoxymethyl



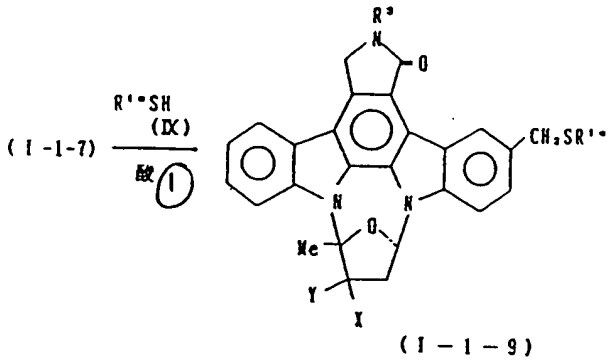

(I-1-8)

Key: 1 Acid

(where X, Y and $R^3$ have the same meanings as above, and $R^{1d}$ represents lower alkyl).

Compound (I-1-8) is formed in a reaction between hydroxymethyl substances (I-1-7) and lower alkyl alcohol (VIII) in an inert solvent and in the presence of an appropriate acid catalyst, such as camphorsulfonic acid. With respect to compound (I-1-8), usually, the amount of compound (VII) is present in significant excess, and the amount of the acid is 1 Eq. Examples of the inert solvents that can be used include chloroform, etc. The reaction is usually carried out with heating under reflux for 5-10 h.

1-9. Compound (I-1-9) with $R^1$ and/or $R^2$ representing alkylthiomethyl

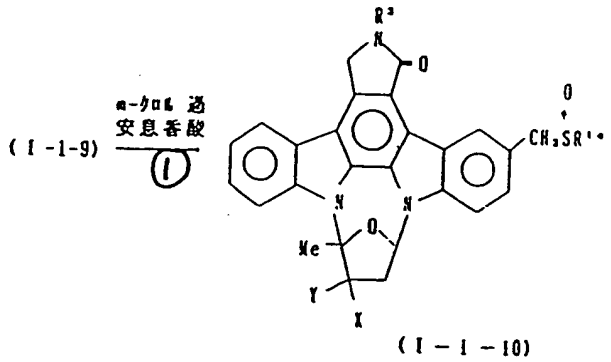



Key: 1 Acid

(where X, Y and $R^3$ have the same meanings as above, and $R^{1e}$ represents lower alkyl).

Compound (I-1-9) is formed in the reaction between hydroxymethyl substance (I-1-7) and lower alkylthiol (IX) in an inert solvent containing an appropriate acid catalyst, such as camphorsulfonic acid. With respect to compound (I-1-7), the amount of compound (IX) used is usually in the range of 5-10 Eq, and the amount of the acid is 1 Eq. Examples of the inert solvents that can be used include chloroform, etc. The reaction is usually carried out at room temperature for 2-3 h.

1-10. Compound (I-1-10) with $R^1$ and/or $R^2$ representing alkylsulfinylmethyl



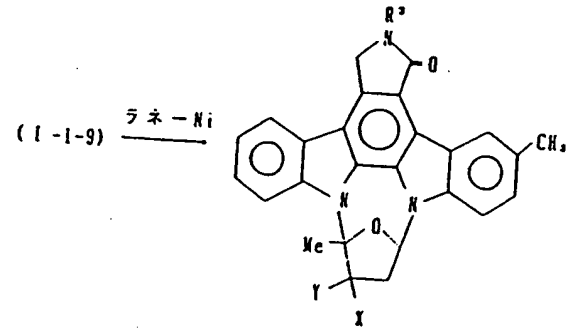

(I-1-10)

Key: 1 m-Chloroperbenzoic acid

(where X, Y $R^3$ and $R^{1e}$ have the same meanings as above).

Compound (I-1-10) is formed by the oxidation of alkylthiomethyl substance (I-1-9) by stirring at room temperature for 1-6 h with 1 Eq of m-chloroperbenzoic acid in chloroform.

1-11. Compound (I-1-11) with $R^1$ and/or $R^2$ representing methyl



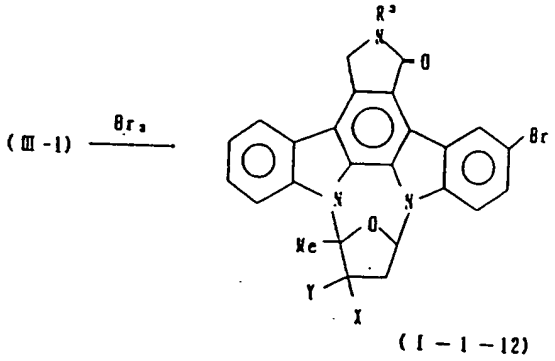

(I-1-11)

Key: 1 Raney Ni

(where X, Y and $R^3$ have the same meanings as above).

Compound (I-1-11) is formed by means of heating alkylthiomethyl substance (I-1-9) under reflux for 5-7 h in the presence of Raney nickel in an amount in the range of 0.1-0.5 times the weight of compound (I-1-9) in ethyl acetate.

1-12. Compound (I-1-12) with $R^1$ and/or $R^2$ representing bromo

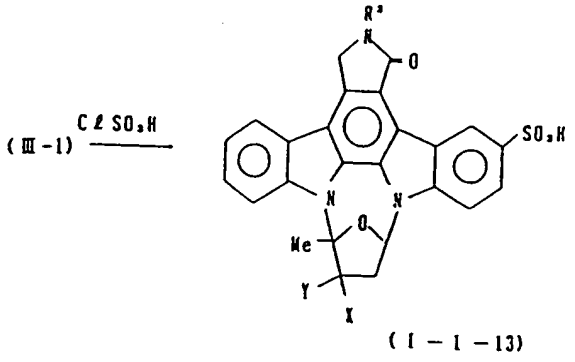



(I-1-12)

(where X, Y and $R^3$ have the same meanings as above).

Compound (I-1-12) is formed by a reaction for 1 day between compound (III-1) and 2-2.5 Eq of bromine by stirring at room temperature in pyridine.

1-13. Compound (I-1-13) with $R^1$ and/or $R^2$ representing sulfonic acid

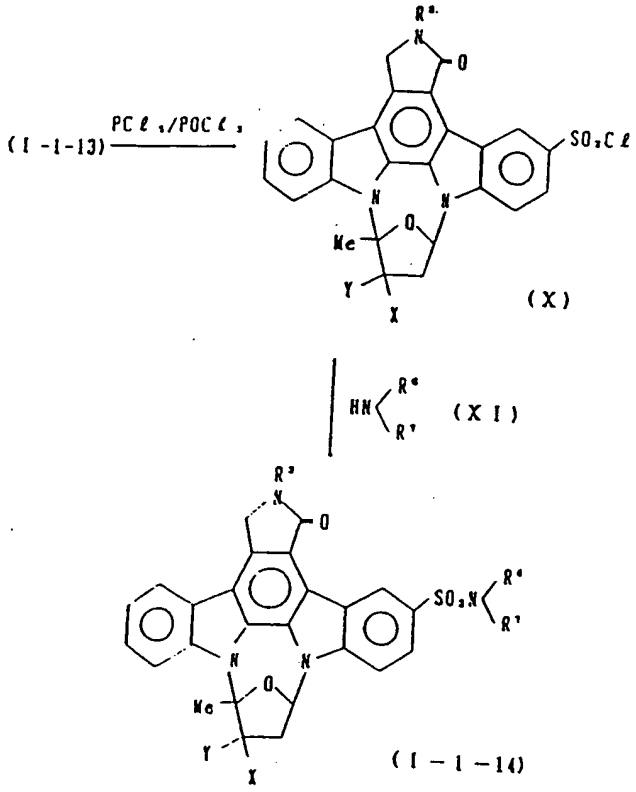



(I-1-13)

(where X, Y and $R^3$ have the same meanings as above).

Compound (I-1-13) is formed in a reaction between compound (III-1) and chlorosulfonic acid in an inert solvent, such as chloroform, in the presence of molecular sieve 4Å. With respect to compound (III-1), the amount of chlorosulfonic acid used is usually in the range of 2-2.5 Eq, and the weight of molecular sieve 4Å used is identical to that of compound (III-1). The reaction is carried out at a temperature in the range of -10°C to 10°C for 1-6 h.

1-14. Compound (1-1-14) with $R^1$ and/or $R^2$ representing amidosulfonate

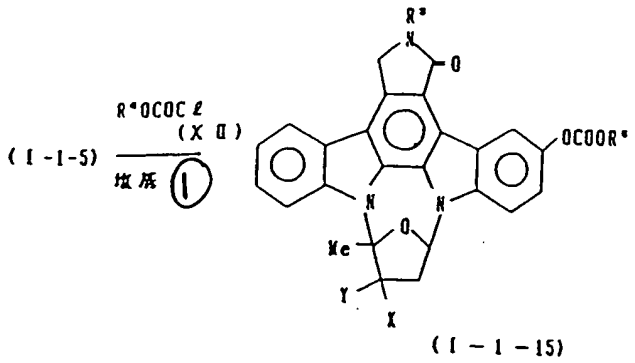



(where X, Y, $R^3$, $R^6$, and $R^7$ have the same meanings as above).

Sulfonic [sic; sulfonyl] chloride (X) is formed in a reaction between sulfonic acid (I-1-13) and phosphorus pentachloride or phosphorus oxychloride with heating under reflux for 1-6 h. With respect to compound (I-1-13), the amount of phosphorus pentachloride used is 2 Eq, and the amount of phosphorus oxychloride used is 10 Eq. Then, compound (I-1-14) is

formed in a reaction between compound (X) and amine (XI) in an inert solvent, such as DMF, forming compound (I-1-14). Examples of bases that can be used include pyridine, triethylamine, etc. With respect to compound (X), the amount of the base used is 2-3 Eq. The amount of compound (XI) used with respect to compound (X) is 4-5 Eq. The reaction is carried out at a temperature in the range of 0°C to room temperature for 1-12 h.

1-15. Compound (1-1-15) with $R^1$ and/or $R^2$ representing -OCOOR$^8$



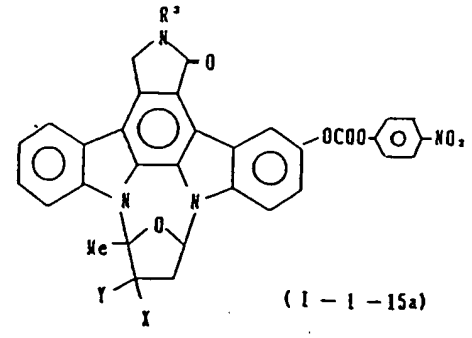

(I-1-15)

Key: 1 Base

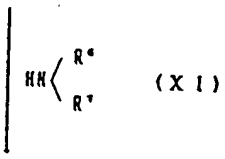
(where X, Y, $R^3$ and $R^8$ have the same meanings as above).

Compound (I-1-15) is formed in a reaction between hydroxy substance (I-1-5) and acid chloride (XII) in the presence of an appropriate type of base, such as triethylamine, in an inert solvent, such as THF. With respect to compound (I-1-5), the amount of compound (XII) used is 1-2 Eq, and the amount of base used is 2-2.5 Eq. The reaction is carried out at a temperature in the range of 0°C to room temperature for 0.5-6 h.

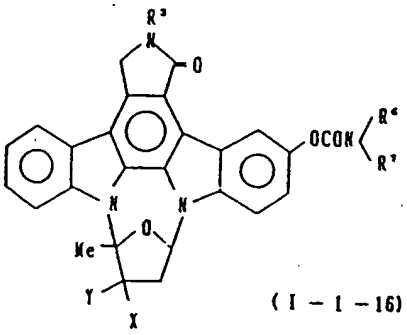
1-16. Compound (1-1-16) with $R^1$ and/or $R^2$ representing $-OCON\langle^{R^6}_{R^7}$




(I-1-15a)




(XI)




(I-1-16)

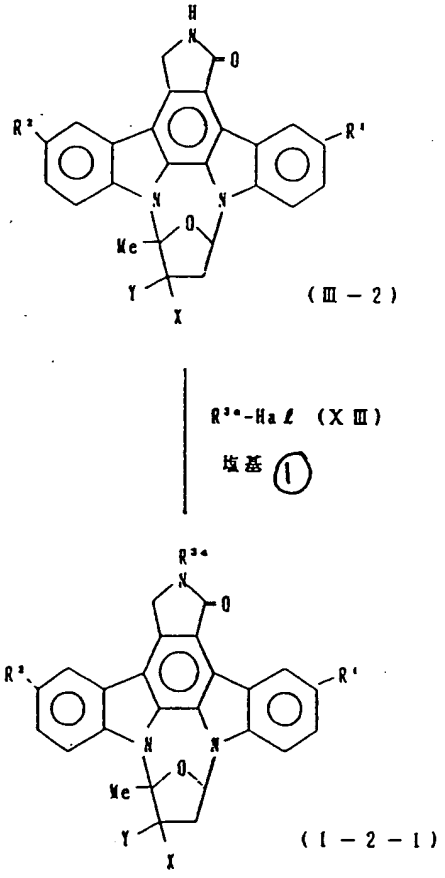
(where X, Y, $R^3$, $R^6$, and $R^7$ have the same meanings as above).

Compound (I-1-16) is formed in a reaction between p-nitrophenoxy substance (I-1-15a) (compound (I-1-15) in which $R^8$ = p-nitrophenoxy) and amine (XI) in an inert solvent, such as DMF. With respect to compound (I-1-15a), the amount of compound

(XI) used is 1-1.2 Eq. The reaction is carried out at a temperature in the range of 0°C to room temperature for 0.5-6 h.

Method 2. Synthesis of compound (I-2) with functional groups in $R^3$

2-1. Compound (I-2-1) with $R^3$ representing alkyl

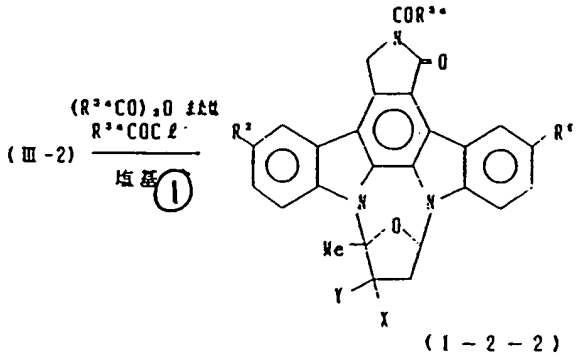


Key: 1 Base

(where X, Y, $R^1$, $R^2$ and Hal have the same meanings as above, and $R^{3a}$ represents lower alkyl).

Compound (I-2-1) is formed in a reaction between compound (III-2) (compound in which $R^3$ in compound (I) represents hydrogen, and compound (II)) and lower alkyl halide (XIII) in an inert solvent in the presence of a base. The preferred types of compound (XIII) include highly reactive iodides and bromides. Examples of the bases that can be used include sodium hydroxide, potassium t-butoxide, etc. With respect to compound (III-2), the amount of compound (XIII) used is usually in the range of 1-3 Eq. Examples of the inert solvents that can be used include DMF and THF. The reaction is carried out at a temperature in the range of 0°C to room temperature for 20 min to 1 h.

2-2. Compound (I-2-2) with $R^3$ representing alkanoyl



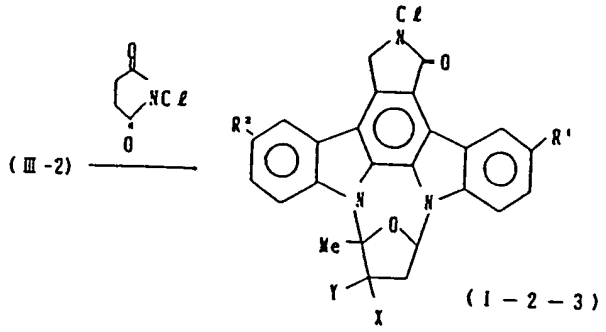

(I-2-2)

Key: 1 Or
2 Base

(where X, Y, $R^1$, $R^2$, and $R^{3a}$ have the same meanings as above).

Compound (I-2-2) is formed in a reaction between compound (III-2) and acylating agent ($(R^{3a}CO)_2O$ or $R^{3a}COCl$, etc.) under the same conditions in method 1-2c.

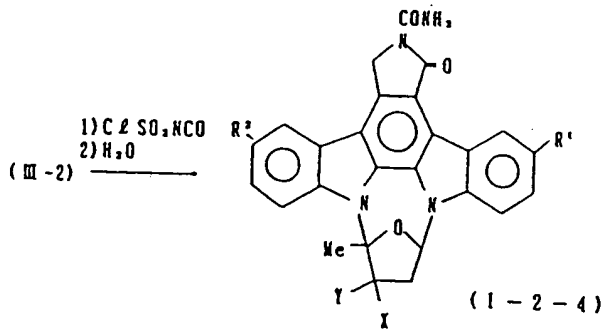
2-3. Compound (I-2-3) with $R^3$ representing chlorine




(where X, Y, $R^1$ and $R^2$ have the same meanings as above).

Compound (I-2-3) is formed in a reaction between compound (III-2) and an appropriate chlorinating agent, such as N-chlorosuccinimide (NCS) in an inert solvent. With respect to compound (III-2), the amount of the chlorinating agent used is usually 1 Eq. Examples of the inert solvents that can be used include chloroform and dichloromethane. The reaction is carried out with heating for 1-24 h.

2-4. Compound (I-2-4) with $R^3$ representing carbamoyl

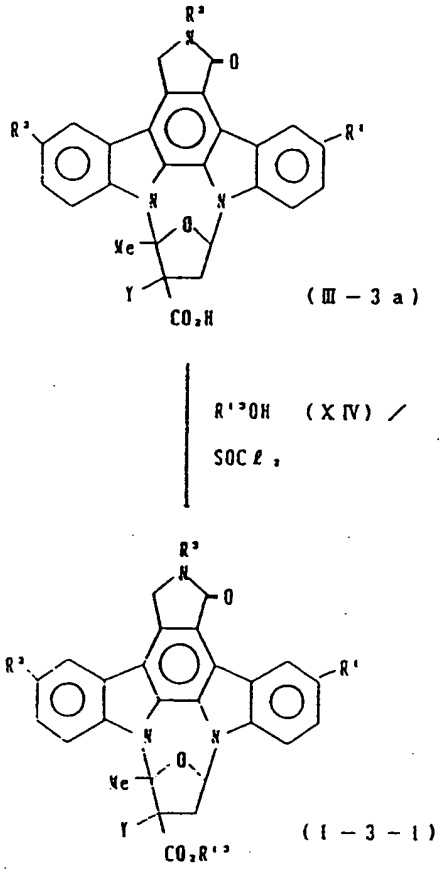



(where X, Y, $R^1$ and $R^2$ have the same meanings as above).

Compound (I-2-4) is formed in a reaction between compound (III-2) and an appropriate carbamoylating agent, such as chlorosulfonyl isocyanate, in an inert solvent, such as THF. The reaction is carried out with stirring under ice cooling for 1-3 h, followed by adding water and then stirring with heating at 70-80°C for 0.5-1 h. With respect to compound (III-2), the amount of the carbamoylating agent used is usually in the range of 1-10 Eq. The amount of water is a significant excess.

Method 3. Synthesis of compound (I-3) with X modified

3-1. Compound (I-3-1) with X representing alkoxycarbonyl

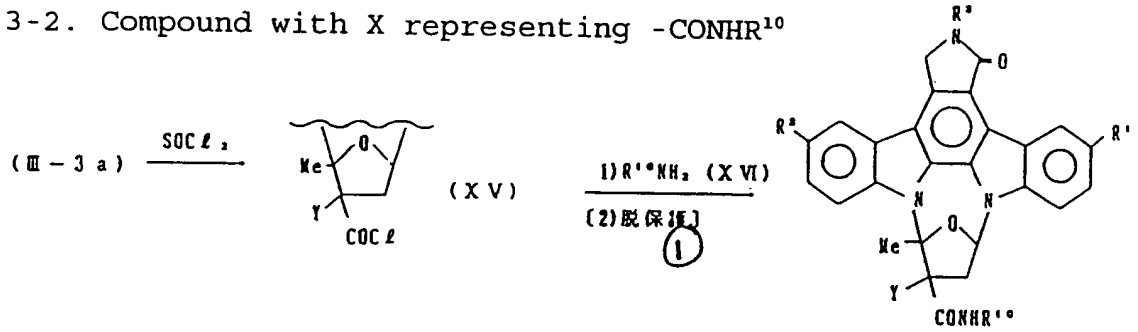



(where X, Y, $R^1$, $R^2$ and $R^3$ have the same meanings as above, and $R^{13}$ represents lower alkyl).

Compound (I-3-1) is formed in a reaction carried out by adding alcohol (XIV) and an excess of thionyl chloride, followed by heating with reflux. The amount of thionyl chloride is

usually about 1/10 (by volume) the amount of compound (XIV), which is also used as the solvent. The reaction is carried out at 80-100°C for 1 h to 1 day.

3-2. Compound with X representing -CONHR$^{10}$




(I-3-2)

Key: 1 Deprotection

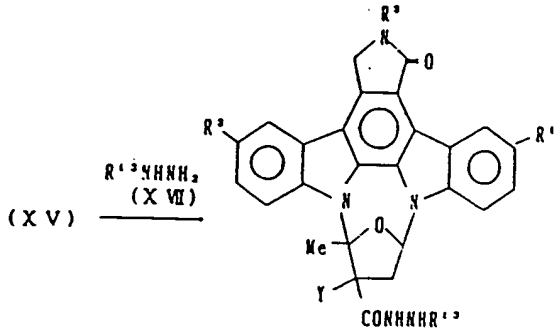
(where X, Y, $R^1$, $R^2$, $R^3$ and $R^{10}$ have the same meanings as above).

Compound (I-3-2) is formed in a reaction between compound (XV) and α-amino acid lower alkyl ester or benzyl ester (XVI) in an inert solvent. With respect to compound (XV), the amount of compound (XVI) is usually about 10 Eq. When the acid salt of compound (XVI), such as hydrochloride salt, is used, it is necessary to add an equimolar amount of a tertiary amine, such as triethylamine. Examples of the solvents that can be used include chloroform, etc. The reaction is carried out at 0°C to room temperature for 1 h to 1 day.

Also, when compound (I-3-2a) with a free carboxyl group of the amino acid is required as compound (I-3-2), it can be prepared by deprotection of ester (I-3-2b) by a conventional method. For example, when compound (I-3-2b) is a lower alkyl ester, compound (I-3-2a) can be prepared by hydrolysis of compound (I-3-2b) at room temperature for 0.5-6 h in aqueous THF with potassium hydroxide. Also, for the benzyl ester, the same

type of compound (I-3-2a) can be formed using the catalytic reduction method described in method (I-2a).

3-3. Compound (I-3-3) with X representing alkylhydrazinocarbonyl

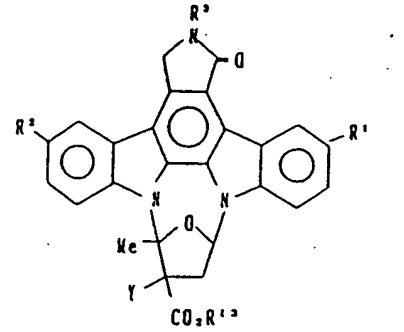


(I-3-3)

(where Y, $R^1$, $R^2$, $R^3$ and $R^{13}$ have the same meanings as above).

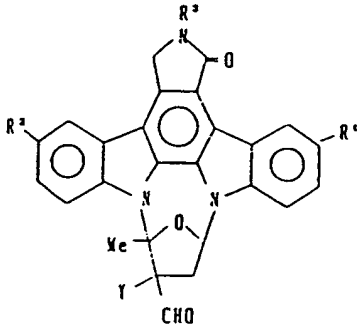
Compound (I-3-3) is formed in a reaction between acid chloride (XV) prepared in method 3-2 and hydrazines (XVII) under the same conditions as in method 3-2.

3-4. Compound (I-3-4) with X representing formyl



(III-3b)

還元 (1)



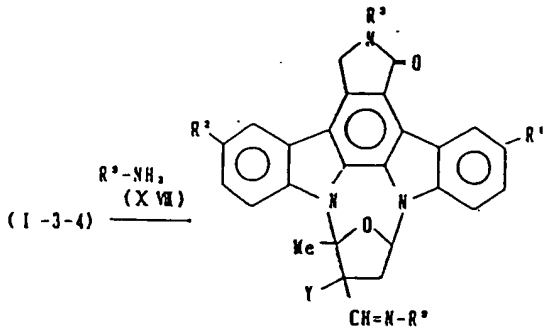
(I-3-4)

Key: 1 Reduction

(where Y, $R^1$, $R^2$ $R^3$ and $R^{13}$ have the same meanings as above).

Compound (I-3-4) is formed in a reaction between compound (III-3b) (compound (I-3-1)) and K-252, as well as an appropriate type of reducing agent, such as lithium aluminum hydride, in THF. The amount of the reducing agent used is usually 1 Eq. The reaction is carried out under ice cooling for 1 h.

3-5. Compound (I-3-5) with X representing -CH=N-$R^9$

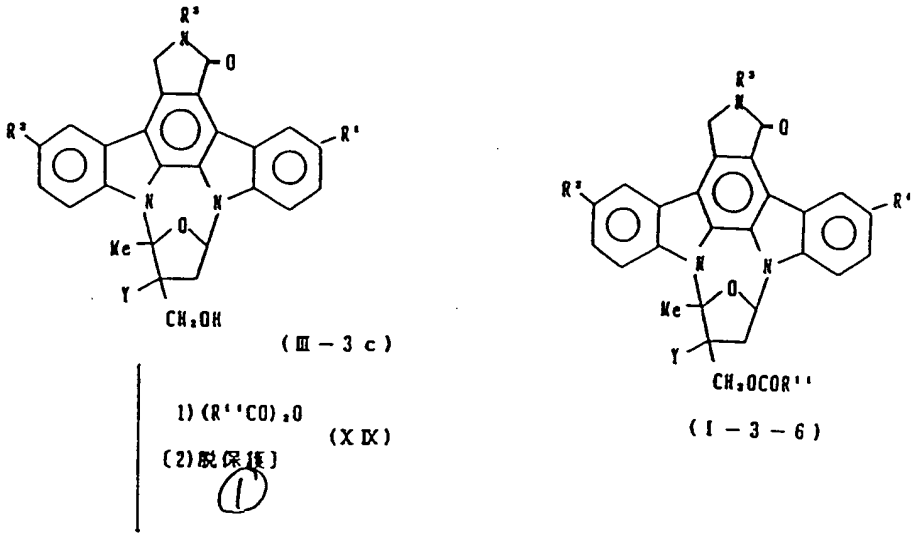



(I-3-5)

(where Y, $R^1$, $R^2$ $R^3$ and $R^9$ have the same meanings as above).

Compound (I-3-5) is formed in a reaction between compound (I-3-4) and amines (XVII) in a mixture of THF and water (10:1). The amount of compound (XVII), which is usually in the form of its hydrochloride salt, hydrobromide salt or sulfate salt, is usually in the range of 5-10 Eq. The reaction is carried out at room temperature for 1 h to 1 day.

3-6. Compound (I-3-6) with X representing $-CH_2OCOR^{11}$




Key: 1 Deprotection

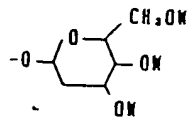
(where Y, $R^1$, $R^2$, $R^3$ and $R^{11}$ have the same meanings as above).

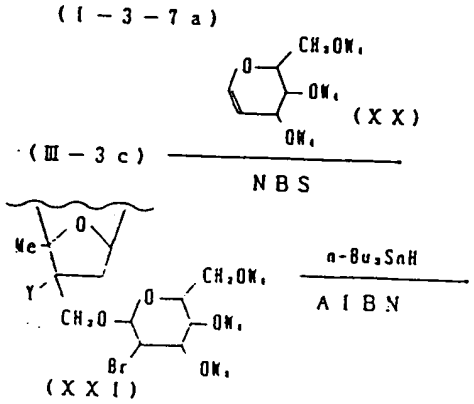
Compound (I-3-6) is formed in a reaction between hydroxymethyl substance (III-3c) (compound with X representing hydroxymethyl in compound (I) and compound (IIb)) and the anhydride (XIX) of an α-amino acid in an appropriate solvent and in the presence of a base. The amount of base, which may be triethylamine, N,N-dimethylaminopyridine, etc., is usually in the range of 1-2.4 Eq with respect to compound (III-3c). The amount of compound (XIX) used is in the range of 1-1.2 Eq with respect to compound (III-3c). Examples of the solvents that can be used include THF, DMF, etc. The reaction is carried out at a

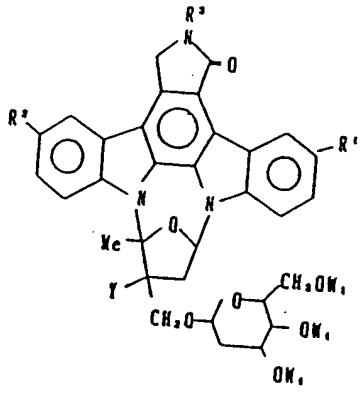
temperature in the range from room temperature to about 100°C for 1-12 h.

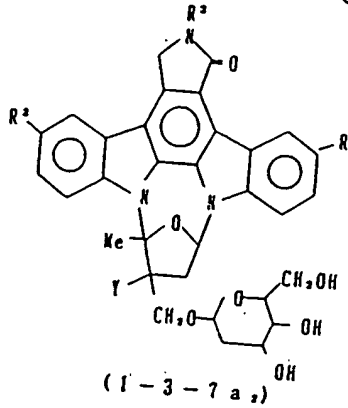
Also, when compound (I-3-6a) with the amino group of amino acid in free form is desired as compound (I-3-6), deprotection may be carried out by a conventional method. For example, when the protecting group is benzyloxycarbonyl, compound (I-3-6a) can be formed using the catalytic reduction method described in method 1-2a.

3-7. Compound (I-3-7) with X representing $-CH_2Z$

3-7a. Compound (1-3-7a) with Z representing 



Key: 1 Deprotection

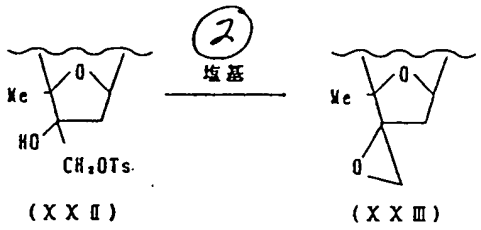
(where $W_1$ represents W, excluding hydrogen in its definition; Y, $R^1$, $R^2$, $R^3$ and W have the same meanings as above).

Chloride (XXI) is formed in a reaction between (III-3c) and tri-O-substituted-glucaric acid (XX) in a solvent inert to the reaction, such as chloroform, and in the presence of N-bromosuccinimide (NBS). With respect to compound (III-3c), the amount of the NBS is in the range of 1-5 Eq, and the amount of compound (XX) is in the range of 1-1.5 Eq. The reaction is usually carried out at room temperature in the dark for 6 h to 1 day.

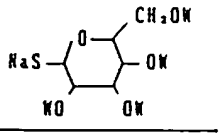
Then, dechlorinated substance (I-3-7a1) is formed in a reaction between compound (XXI) and tributyltin hydride in the presence of $\alpha,\alpha'$-azobisisobutyronitrile (AIBN) in a solvent inert to the reaction, such as toluene. The amounts of tributyltin hydride and AIBN should be in the range of 1.5-2 Eq with respect to compound (XXI). The reaction is usually carried out at 60-100°C for 1-12 h.

Also, when compound (I-3-$7a_2$) with W representing hydrogen is desired as compound (I-3-7a), deprotection may be carried out using the conventional method for the protecting group in compound (I-3-$7a_1$). For example, when $W_1$ represents acetyl in compound (I-3-$7a_1$), it is possible to form compound (I-3-$7a_2$) by reacting said compound (I-3-$7a_1$) with 3-6 Eq of sodium hydroxide or aqeous ammonia in aqueous THF at room temperature for 1-12 h. Also, when $W_1$ represents benzyl, the catalytic reduction method described in method 1-2a can be used.

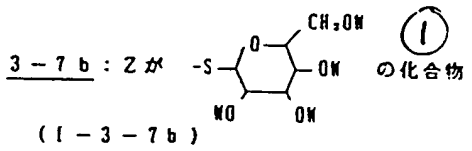
3-7b. Compound (1-3-7b) with Z representing [a] [see orig. p. 16]



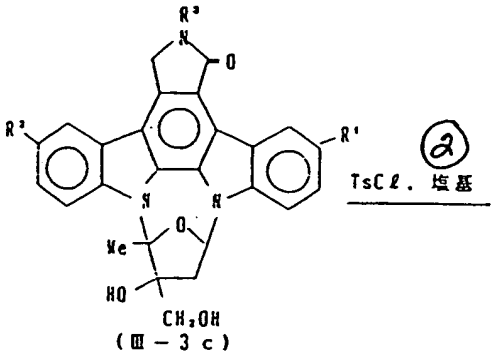

(ＸＸⅡ) (ＸＸⅢ)



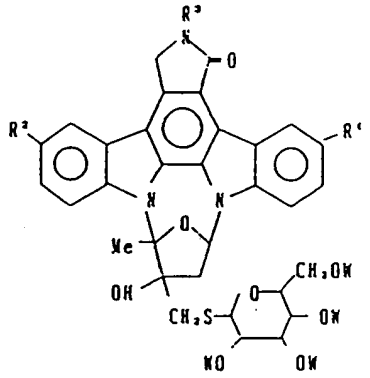

(ＸＸⅣ)




(Ⅰ－3－7ｂ)




(Ⅲ－3ｃ)




(Ⅰ－3－7ｂ)

Key: 1 Deprotection
2 Base

(where $R^1$, $R^2$, $R^3$, and W have the same meanings as above).

First of all, tosyl substance (XXII) is formed in a reaction between hydroxymethyl substance (III-3c)' (compound with Y representing hydroxy in compound (III-3c)) and p-toluenesulfonyl chloride (TsCl) in a solvent inert to the reaction and in the presence of a base. Examples of the bases that can be used include triethylamine, pyridine, N,N-dimethylaminopyridine, sodium hydride, etc. Examples of the inert solvents that can be used include THF, dioxane, chloroform, etc. With respect to compound (III-3c)', the amounts of p-toluenesulfonyl chloride and base are in the range of 2-3 Eq. The reaction is usually carried out at a temperature in the range of 0°C to room temperature for 1 h to 1 day.

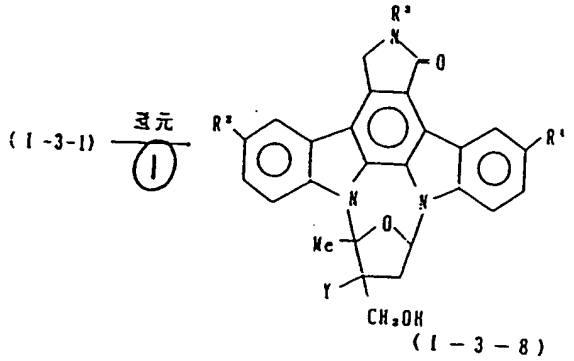
Then, epoxide (XXIII) is formed in a reaction between compound (XXII) and 1-2 Eq of sodium hydride. The reaction is usually carried out in THF or dioxane at room temperature for 1-6 h.

Also, compound (1-3-7b) is formed in a reaction between compound (XXIII) and thioglucose sodium salt (XXIV) in an inert solvent, such as DMF.

With respect to compound (XXIII), the amount of compound (XXIV) used is in the range of 1-1.5 Eq. The reaction is usually carried out at a temperature in the range from room temperature to 50°C for 1-12 h.

3-8. Compound (I-3-8) with X representing hydroxymethyl

Compound (I-3-8) with X representing hydroxymethyl may be prepared from compound (IIb) as the starting material, or it may be prepared by reducing alkoxycarbonyl compound (I-3-1).



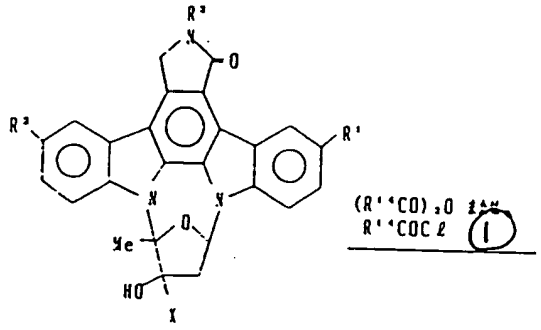

Key: 1 Reduction

(where Y, $R^1$, $R^2$ and $R^3$ have the same meanings as above).

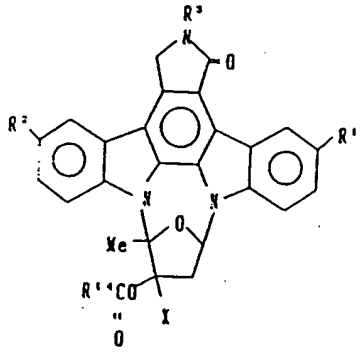
Compound (1-3-8) is formed in a reaction between compound (I-3-1) and an appropriate type of reducing agent, such as sodium borohydride, in an appropriate type of inert solvent, such as aqueous THF. The amount of the reducing agent used is in the range of 3-5 Eq. The reaction is usually carried out under ice cooling for 1-6 h.

Method 4. Synthesis of compound (I-4) with Y modified

4-1. Compound (I-4-1) with Y representing alkanoyloxy



(III-4a)



(I-4-1)

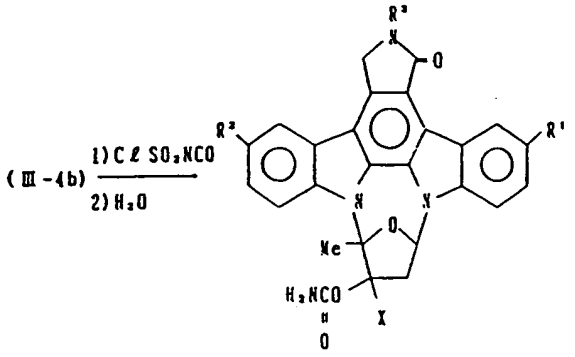
Key: 1 Or

(where X, $R^1$, $R^2$ and $R^3$ have the same meanings as above and $R^{14}$ is lower alkyl).

Compound (1-4-1) is formed in a reaction between hydroxy substance (III-4a) (compound with Y representing hydroxy in compound (I)) and an acylating agent ($(R^{14}CO)_2O$ or $R^{14}COCl$) in the presence of a base. Examples of bases include pyridine, triethylamine, etc. The amount of the acylating agent used is in the range of 1-2 Eq with respect to compound (III-4a). The

reaction is usually carried out in pyridine as the solvent at room temperature for 1-12 h.

4-2. Compound (I-4-2) with Y representing carbamoyloxy

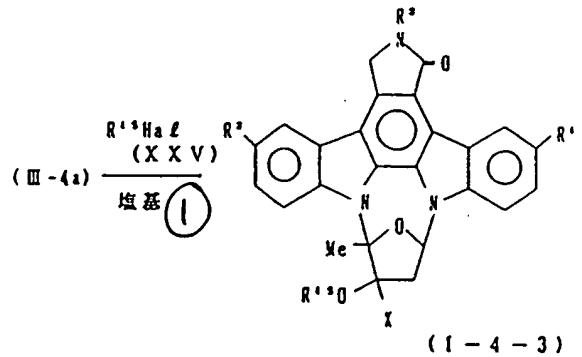



(I-4-2)

(where X, $R^1$, $R^2$, and $R^3$ have the same meanings as above).

Compound (1-4-2) is formed in a reaction between compound (III-4b) (compound (III-4a) and compound (II)) and a carbamoylating reagent, such as chlorosulfonyl isocyanate, under the same conditions as those in method 2-4.

4-3. Compound (I-4-3) with Y representing alkoxy




(I-4-3)

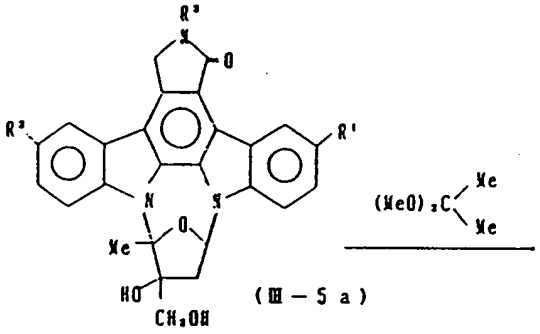
Key: 1 Base

(where X, $R^1$, $R^2$, $R^3$, and Hal have the same meanings as above and $R^{15}$ represents alkyl).

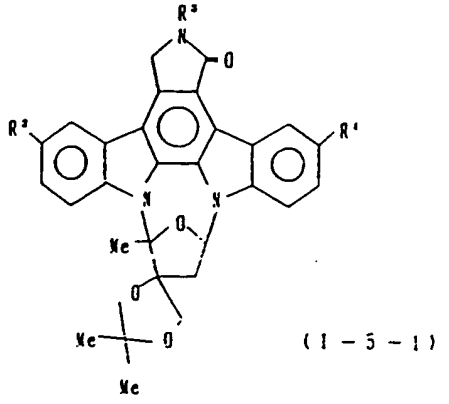
Alkyl substance (I-4-3) can be formed in a reaction between compound (III-4a) and lower alkyl halide (XXV) in an inert solvent in the presence of sodium hydroxide, potassium t-butoxide or another base. The preferable type of compound (XXV) is the highly reactive iodide or bromide. The amounts of compound (XXV) and base used with respect to compound (III-4a) is 1 Eq. Examples of the inert solvents include DMF, THF, etc. The reaction is usually carried out at a temperature in the range from 0°C to room temperature for 20 min to 1 h.

Method 5. Synthesis of -Y-X- compound (I-5)

5-1. Compound (I-5-1) with -Y-X- representing $-O-C(CH_3)_2-O-CH_2-$



(III-5a)

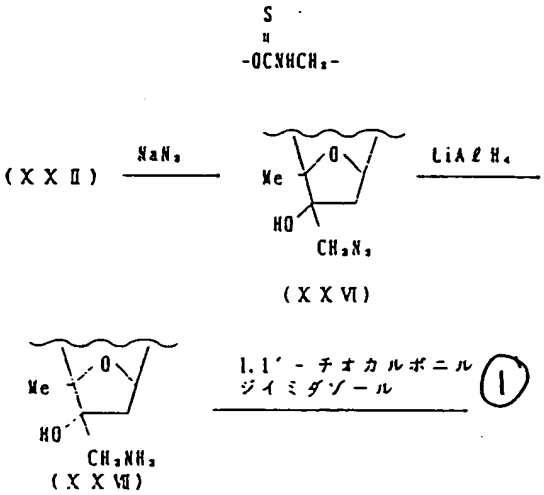


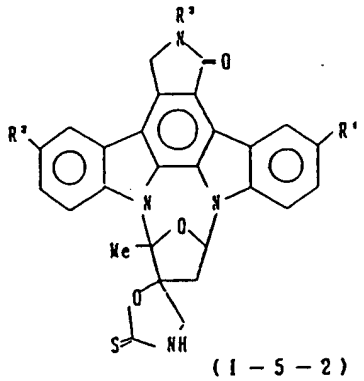
(I-5-1)

(where $R^1$, $R^2$ and $R^3$ have the same meanings as above).

Compound (I-5-1) is formed in a reaction between compound (III-5a) (compound (I) with X representing hydroxymethyl and with Y representing hydroxy; also [designated] compound (IIb)) and 2,2-dimethoxypropane, usually in an amount of 5 Eq, in chloroform in the presence of an appropriate type of acid catalyst, such as camphorsulfonic acid (in an amount of 0.1-0.5 Eq with respect to compound (III-5a)), with heating under reflux for 1-12 h.

5-2. Compound (I-5-2) with -Y-X representing




(I-5-2)

Key: 1 1,1'-Thiocarbonyldiimidazole

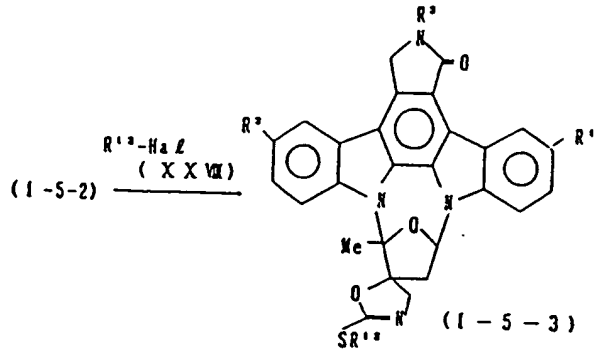
(where $R^1$, $R^2$ and $R^3$ have the same meanings as above).

In the reaction, first of all, azide substance (XXVI) is formed in a reaction between the tosyl substance (XXII) prepared in method 3-7b and sodium azide, usually with an amount in the range of 1-2 Eq, in an inert solvent. Examples of the inert solvents that can be used include DMF, dimethyl sulfoxide, THF, etc. The reaction is usually carried out at room temperature for 1 h to 1 day.

Then, amine substance (XXVII) is formed in a reaction between compound (XXVI) and 2-6 Eq of lithium aluminum hydride in an inert solvent. Examples of the inert solvents that can be used include THF, dioxane, etc. The reaction is usually carried out at a temperature in the range from 0°C to room temperature for 1-6 h.

Then, compound (I-5-2) is formed in a reaction between compound (XXVII) and 1-2 Eq of 1,1'-thiocarbonyldiimidazole in DMF under ice cooling for 1-2 h.

5-3. Compound (I-5-3) with -Y-X representing $-O-\overset{SR^{12}}{\overset{|}{C}}=N-CH_2-$




(where $R^1$, $R^2$, $R^3$, $R^{12}$ and Hal have the same meanings as above).

Compound (I-5-3) is formed in a reaction between compound (I-5-2) obtained in method (5-2) and lower alkyl halide (XXVII) in DMF. The preferable type of compound (XXVII) is the highly reactive iodide. The reaction is usually carried out at room temperature for 1-12 h.

As explained above, by implementing methods 1-5 in an appropriate combination, it is possible to form compound (I) with the desired functional groups at the desired positions.

After the aforementioned process of operation, the product is isolated and refined using the conventional methods adopted in the organic synthesis, such as extraction, crystallization, chromatography, etc., which may be combined appropriately.

Compound (I) and its pharmacologically tolerable salts have not only excellent C-kinase inhibiting activity, but also excellent inhibiting effect in preventing the liberation of

histamine, preventing coagulation of blood platelets, preventing inflammation, etc. Consequently, they are expected to find application as the active ingredient in drugs. The drug formulations prepared in this case usually contain an effective dose of compound (I) or its pharmacologically tolerable salt and at least one type of pharmacologically tolerable medicinal vehicle. The dose of the drug formulation depends on the administration method, treatment period, age, substance weight, etc., and the daily dose is usually in the range of 0.5-1 mg/kg of the substance weight of the patient in case of oral or nonoral administration (such as injection, liniment, inhalation, etc.) Various forms can be adopted for the formulations, such as tablets, pills, powder, granules, capsules, ointment, solution for injection, etc. Examples of the medicinal vehicles that can be used for forming the formulations include lactose, dextrose, sucrose, sorbitol, mannitol, glucose, cyclodextrin, talc, starch, methylcellulose, gelatin, gum arabic, polyethylene glycol, carboxymethylcellulose, hydroxypropylcellulose, sodium benzoate, sodium hydrogen sulfite, aluminum stearate, magnesium stearate, vegetable oils, white vaseline, for distilled water injection, etc., which can be selected appropriately for use. The formulation contains 0.01-85 wt% of compound (I) or its pharmacologically tolerable salt.

In addition, compound (I) has displayed significant activity in inhibiting the growth of cancerous cells, such as human cervical cancer cells (Hela cells), human breast cancer cells MCF7, human colon cancer cells COLO 320 DM, human lung differentiated squamous cancer cells PC-10, etc. Consequently,

compound (I) can be used as an effective ingredient in antineoplastic drugs.

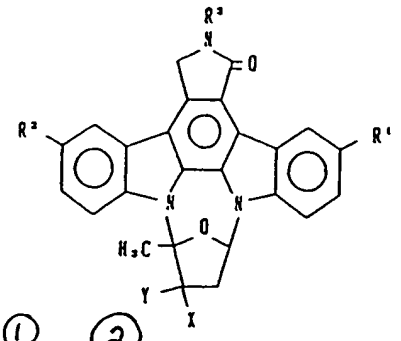
When compound (I) is to be administered as an antineoplastic drug, with a dose in the range of 0.01-20 mg/kg, the compound is usually administered by means of intraveneous injection in the form of an injection solution prepared by dissolving it in physiological saline containing glucose, lactose and mannitol. Also, it is possible to perform freeze-drying based on the method defined in the Japanese Pharmacopoeia. Also, it may be blended with sodium chloride to form a powdered injection agent. Also, it may blended with salts as required for medical application, such as the pharmacologically tolerable diluents, adjuvants, and/or vehicle. When it is used as an injection solution, it is preferred that an adjuvant be used at the same time for increasing the solubility. The dose should be selected appropriately according to the age and symptoms of the patient. The administration schedule can be adjusted according to the symptoms and the dose. Usually, it is administered once daily (for a single time or consecutively for several days), 1-3 times weekly, or once in three weeks in an intermittent manner. The drug can be administered either orally or rectally. With oral administration, appropriate types of adjuvants can be added, and the forms of the drug include tablets, powder, granules, syrup, ointment, etc.

Application examples

Table I lists the typical examples of compounds (I) prepared using the aforementioned manufacturing methods. Table II lists

the corresponding intermediate substances. The manufacturing examples of compounds (I) are presented in the application examples; the manufacturing examples of the intermediate substances are presented in the reference examples; the pharmacological activities of typical compounds (I) are shown in the experimental examples, and examples of formulations of typical compounds (I) are shown in the reference examples.

Table I



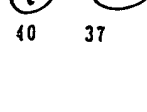
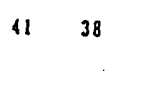
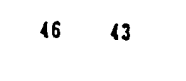
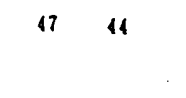
(I)

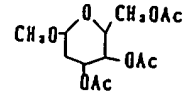
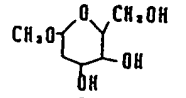
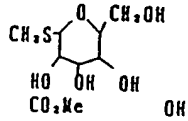
| ①化合物 No. | ②实施例 No. | R' | R² | R³ | X | Y | ③塩 |
|---|---|---|---|---|---|---|---|
| 1 | 1 | $NH_2$ | H | Ac | $CO_2Me$ | OAc | |
| 2 | 1 | $NH_2$ | $NH_2$ | Ac | $CO_2Me$ | OAc | |
| 3 | 2 | $NH_2$ | H | H | $CO_2Me$ | OH | HCℓ |
| 4 | 3 | $NH_2$ | $NH_2$ | H | $CO_2Me$ | OH | |
| 5 | 4 | $NMe_2$ | H | H | $CO_2Me$ | OH | HCℓ |

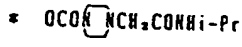
| ① 化合物 No. | ② 実施例 No. | R¹ | R² | R³ | X | Y | ③ 塩 |
|---|---|---|---|---|---|---|---|
| 6 | 5 | $NEt_2$ | H | H | $CO_2Me$ | OH | HCℓ |
| 7 | 6 | NHAc | H | Ac | $CO_2Me$ | OAc | |
| 8 | 7 | NHAc | H | H | $CO_2Me$ | OH | |
| 9 | 8 | NHCOn-Pr | H | Ac | $CO_2Me$ | OAc | |
| 10 | 9 | NHCOn-Pr | H | H | $CO_2Me$ | OH | |
| 11 | 10 | NHCOn-Bu | H | Ac | $CO_2Me$ | OAc | |
| 12 | 11 | NHCOn-Bu | H | H | $CO_2Me$ | OH | |
| 13 | 12 | NHCONHMe | H | H | $CO_2Me$ | OH | |
| 14 | 13 | NHCONHEt | H | H | $CO_2Me$ | OH | |
| 15 | 14 | NHCONHPh | H | H | $CO_2Me$ | OH | |
| 16 | 15 | $NHCONH_2$ | H | H | $CO_2Me$ | OH | |
| 17 | 16 | COMe | H | Ac | $CO_2Me$ | OAc | |
| 18 | 16 | COMe | COMe | Ac | $CO_2Me$ | OAc | |
| 19 | 17 | CHO | H | Ac | $CO_2Me$ | OAc | |
| 20 | 17 | CHO | CHO | Ac | $CO_2Me$ | OAc | |
| 21 | 18 | COMe | H | H | $CO_2Me$ | OH | |
| 22 | 19 | CHO | H | H | $CO_2Me$ | OH | |
| 23 | 20 | CHO | CHO | H | $CO_2Me$ | OH | |

| ① 化合物 No. | ② 実施例 No. | R¹ | R² | R³ | X | Y | ③ 塩 |
|---|---|---|---|---|---|---|---|
| 24 | 21 | OH | H | H | $CO_2Me$ | OH | |
| 25 | 22 | OH | OH | H | $CO_2Me$ | OH | |
| 26 | 23 | OMe | H | H | $CO_2Me$ | OH | |
| 27 | 24 | OEt | H | H | $CO_2Me$ | OH | |
| 28 | 25 | On-Pr | H | H | $CO_2Me$ | OH | |
| 29 | 26 | Oi-Pr | H | H | $CO_2Me$ | OH | |
| 30 | 27 | On-Bu | H | H | $CO_2Me$ | OH | |
| 31 | 28 | $CH_2OH$ | H | Ac | $CO_2Me$ | OAc | |
| 32 | 29 | $CH_2SEt$ | H | Ac | $CO_2Me$ | OAc | |
| 33 | 30 | Me | H | Ac | $CO_2Me$ | OAc | |
| 34 | 31 | $CH_2SEt$ | H | H | $CO_2Me$ | OH | |
| 35 | 32 | Me | H | H | $CO_2Me$ | OH | |
| 36 | 33 | $CH_2S(O)Et$ | H | H | $CO_2Me$ | OH | |
| 37 | 34 | Br | H | H | $CO_2Me$ | OH | |
| 38 | 35 | H | H | H | CONHNHMe | OAc | |
| 39 | 36 | H | H | H | $CONHCH_2CO_2Me$ | OAc | |

Key: 1 Compound
2 Application example
3 Salt

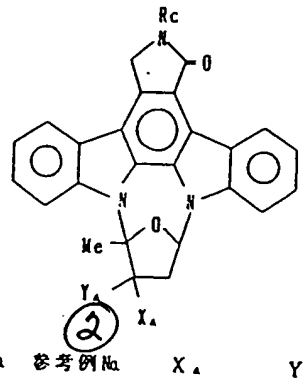
| 化合物 No. (1) | 実施例 No. (2) | R¹ | R² | R³ | X | Y | 塩 (3) |
|---|---|---|---|---|---|---|---|
| 40 | 37 | H | H | H |  | OAc | |
| 41 | 38 | H | H | H |  | OAc | $NH_3$ |
| 42 | 39 | H | H | H | $CONHCH_2CO_2H$ | OH | $NH_3$ |
| 43 | 40 | H | H | H | CHO | OH | |
| 44 | 41 | H | H | H | CH=NOH | OH | |
| 45 | 42 | H | H | H | $CH=NNHCONH_2$ | OH | |
| 46 | 43 | H | H | H |  | OH | |
| 47 | 44 | H | H | H |  | OH | |
| 48 | 45 | H | H | Me | $CO_2Me$ | OMe | |
| 49 | 46 | H | H | Cℓ | $CO_2Me$ | OH | |
| 50 | 47 | H | H | H | $-CH_2NHC(=S)-O-$ | | |
| 51 | 48 | H | H | H | $-CH_2N=C(SMe)-O-$ | | |
| 52 | 49 | H | H | H | $-CH_2-O-C(CH_3)_2-O-$ | | |

| ① 化合物 No. | ② 実施例 No. | $R^1$ | $R^2$ | $R^3$ | X | Y | ③ 塩 |
|---|---|---|---|---|---|---|---|
| 53 | 50 | $NO_2$ | H | H | $CO_2Me$ | OH | |
| 54 | 51 | H | H | $CONH_2$ | $CO_2Me$ | $OCONH_2$ | |
| 55 | 52 | H | H | H | $CH_2OCOCH_2NHCbz$ | OH | |
| 56 | 53 | H | H | H | $CH_2OCOCH_2NH_2$ | OH | HCℓ |
| 57 | 54 | H | H | H |  | OH | |
| 58 | 55 | H | H | H |  | OH | |
| 59 | 56 | H | H | H |  | OH | |
| 60 | 57 | $SO_2H$ | H | H | $CO_2Me$ | OH | |
| 61 | 58 |  | H | H | $CO_2Me$ | OH | |
| 62 | 59 |  | H | H | $CO_2Me$ | OH | |
| 63 | 60 | * | H | H | $CO_2Me$ | OH | |
| 64 | 61 | $CH_2OEt$ | H | Ac | $CO_2Me$ | OAc | |
| 65 | 62 | $CH_2OEt$ | H | H | $CO_2Me$ | OH | |
| 66 | 63 | $CH_2OEt$ | H | H | $CH_2OH$ | OH | |

* 

Key: 1 Compound
2 Application example
3 Salt

Table II Intermediate substances.



| 化合物No. ① | 参考例No. ② | $X_A$ | $Y_A$ | $R_c$ |
|---|---|---|---|---|
| a | 1 | $CO_2Et$ | OH | H |
| b | 2 | $CO_2Me$ | OMe | H |
| c | 3 | $CO_2H$ | OAc | H |
| d | 4 | $COCl$ | OAc | H |
| e | 5 | $CH_2OH$ | OH | H |
| f | 6 | $CH_2OTs$ | OH | H |
| g | 7 | $CH_2N_3$ | OH | H |
| h | 8 | $CH_2NH_2$ | OH | H |
| i | 9 | $CO_2Me$ | OAc | Ac |
| j | 10 | — $CH_2O$ — | | H |

Key: 1 Compound
2 Reference example

Application Example 1

5.51 g (10 mmol) of compound i )III-1; X = $CO_2Me$, Y = OAc, $R^3$ = Ac) prepared in Reference Example 9 were dissolved in 100 mL

of sulfolane and 50 mL of chloroform, followed by the addition of 2.8 g (10.5 mmol) of nitronium tetrafluoroborate. The mixture was heated at 80°C for 2 h. After chloroform was removed under reduced pressure, 200 mL of water were added, and the residue was removed by suction. Then, water and methanol were used in washing, forming a mixture of N,O-diacetylnitro substance (I-1-1; X = $CO_2Me$, Y = OAc, $R^3$ = Ac) and N,O-diacetyldinitro substance (I-1-1′; X = $CO_2Me$, Y = OAc, $R^3$ = Ac).

The aforementioned mixture was dissolved in 250 mL of DMF. Then, 2 g of 10% palladium/carbon were added, followed by stirring at room temperature in a hydrogen gas stream for 2 h. Then, the reaction solution was filtered through Celite, followed by removal of the solvent by distillation under reduced pressure. The residue was refined by silica gel chromatography (with chloroform used as the eluting solvent), followed by recrystallization from a solvent mixture of chloroform and ether (in the following application examples, the solvent mixture used in the recrystallization process refers to two or more types of solvents used), forming 1.74 g (30%) of compound 1 in the form of yellow acicular crystals with a melting point of >300°C, and 0.59 g (10%) of compound 2 in the form of a yellow powder with a melting point of >300°C.

Compound 1: NMR(CDCℓ₃) δ : 1.79(s, 3H), 2.12 (dd, 1H, J=5.14Hz), 2.28(s, 3H), 2.83(s, 3H), 3.98(dd, 1H, J=7.14Hz), 4.03(s, 3H), 5.36(s, 2H), 6.83-7.10(m, 2H), 7.23-7.66(m, 3H), 7.93(dd, 1H, J=2.8Hz), 8.60(dd, 1H, J=2.8Hz), 8.54(d, 1H, J=2Hz)

MS(m/e) : 5 6 7 (M+1)

Compound 2:

NMR(CDCℓ$_3$) δ : 1.74(s, 3H), 2.08 (dd, 1H, J=5.8Hz), 2.15(s, 3H), 2.71(s, 3H), 3.83 (dd, 1H, J=7.14Hz), 3.93(s, 3H), 5.00(br. s, 4H), 5.32(s, 2H), 6.80-7.20(m, 3H), 7.28(br. s, 1H), 7.67(d, 1H, J=8Hz), 7.70(d, 1H, J=8Hz), 8.33(d, 1H, J=2Hz)

MS(m/e) : 582 (M+1)

Application Example 2

700 mg (1.22 mmol) of compound 1 were dissolved in 35 mL of dichloromethane, followed by addition of 1.2 mL (6.1 mmol) of 28% solution of sodium methylate in methanol. Five minutes later, a 3N aqueous solution of hydrochloric acid was added. After the solvent was removed under reduced pressure, the residue was refined by silica gel chromatography (chloroform/methanol/DMF, 80:10:10), followed by recrystallization from chloroform/ether, forming 507 mg (80%) of compound 3 in the form of yellow acicular crystals with a melting point of >300°C.

NMR (DMSO-d) δ : 2.09(dd, 1H, J=5.14Hz), 2.18 (s, 3H), 3.44(dd, 1H, J=7.14Hz), 3.96(s, 3H), 5.09(s, 2H), 6.48(s, 1H), 7.24(dd, 1H, J=5.7Hz), 7.18-7.71(m, 3H), 7.74-8.24(m, 3H), 8.77(s, 1H), 9.30(d, 1H, J=2Hz)

MS(m/e) : 483 (M+1)

Application Example 3

Using the same method as in Application Example 2, from 150 mg (0.26 mmol) of compound 2, 53 mg (41%) of compound 4, in the form of dark brown powder with a melting point of >300°C, were formed.

NMR (DMSO-d) δ : 1.93(dd, 1H, J=5.14Hz), 2.10 (s, 3H), 3.36(dd, 1H, J=7.14Hz), 3.94(s, 3H), 4.96(br. s, 2H), 6.48-7.16(m, 3H), 7.24(d, 1H, J= 2Hz), 7.64(d, 1H, J=2Hz), 7.72(d, 1H, J=2Hz), 8.62(d, 1H, J=2Hz)

MS(m/e) : 498 (M+1)

Application Example 4

155 mg (0.3 mmol) of compound 3 were dissolved in a mixture of 3 mL of methanol and 3 mL of THF. Then, 1 mL of a 35% aqueous solution of formaldehyde was added, followed by the addition of 0.3 mmol of sodium cyanoborohydride. The mixture was stirred at room temperature for 1 h. After a 10% aqueous solution of hydrochloric acid was added to adjust pH to 1, the sample was washed by saturated saline, and then dried with anhydrous magnesium sulfate, After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (with 50 % methanol/chloroform used as the eluting solvent), followed by recrystallization using a solvent mixture of chloroform/ether/methanol, forming 50 mg (31%) of compound 5

in the form of a dark brown powder with a melting point of >300°C.

NMR(DMSO-$d_6$) $\delta$ : 2.03(dd, 1H, J=5.14Hz), 2.16 (s, 3H), 3.20-3.50(1H), 3.40(6H), 3.93(s, 3H), 5.01(d, 1H, J=17), 5.07(d, 1H, J=17Hz), 7.22(dd, 1H, J=5.7Hz), 7.36-7.53(m, 2H), 7.90-8.15(m, 4H), 8.75(s, 1H), 9.44(s, 1H)

MS(m/e) : 5 1 0 (M+)

Application Example 5

Using the same method as in Application Example 4, from 140 mg (0.37 mmol) of compound 3 and 0.17 mL of acetaldehyde, 38 mg (24%) of compound 6, in the form of a dark brown powder with a melting point of >300°C, were formed.

NMR(DMSO-$d_6$) $\delta$ : 1.10(t, 6H, J=7Hz), 2.10(dd, 1H, J=4.3, 13.3Hz), 2.15(s, 3H), 3.50-3.90(m, 4H), 3.93(s, 3H), 5.02-5.08(m, 2H), 6.42(s, 1H), 7.24-7.26(m, 1H), 7.39(t, 1H, J=7Hz), 7.52(t, 1H, J=7Hz), 7.90-8.22(m, 4H), 8.75(br. s, 1H), 9.40 (br. s, 1H)

MS(m/e) : 5 3 9

Application Example 6

1.8 g (3.1 mmol) of compound 1 were dissolved in 50 mL of pyridine. Then, 3 mL of acetic anhydride were added. The mixture was stirred at room temperature for 3 h. After the solvent was removed by distillation under reduced pressure, the residue was blended with chloroform, then washed with a 5% aqueous solution of hydrochloric acid and saturated saline and dried with anhydrous magnesium sulfate. The residue was refined by silica gel chromatography (with 0.5% methanol/chloroform used as the eluting solvent), followed by recrystallization from a solvent mixture of methanol/DMF, forming 1.7 g (90%) of compound 7 in the form of a brown powder with a melting point of >300°C.

NMR(DMSO-$d_6$) $\delta$ : 1.70(s, 3H), 2.0-2.36(1H), 2.10(s, 3H), 2.21(s, 3H), 2.64(s, 3H), 3.76-4.04 (1H), 3.96(s, 3H), 5.43(s, 2H), 7.29(dd, 1H, J=6.8Hz), 7.53(d, 1H, J=8Hz), 7.63(d, 1H, J=8Hz), 7.90-8.20(m, 4H), 9.14(s, 1H), 10.12(s, 1H)

MS(m/e) : 567 ($M^+$-Ac+1)

Application Example 7

Using the same method as in Application Example 2 (using DMF as the solvent), from 0.7 g (1.15 mmol) of compound 7, 0.43 g (71.3%) of compound 8, in the form of brown acicular crystals

with a melting point of >300°C (recrystallized from pyridine/chloroform/ether), were formed.

NMR (DMSO-$d_6$ + $CD_3OD$) $\delta$ : 2.13 (dd, 1H, J=6.14 Hz), 2.18 (s, 3H), 2.23 (s, 3H), 3.52 (dd, 1H, J=7.14Hz), 4.02 (s, 3H), 5.09 (s, [illegible] J=6.7Hz), 7.36-8.20 (m, 6H), [illegible]

MS (m/e) : 524 ($M^+$)

Application Example 8

Using the same method as in Application Example 6, from 100 mg (0.17 mmol) of compound 1 and 15 mg (0.88 mmol) of propionic anhydride, 9.50 mg (47.3%) of compound 9, in the form of red-brown prismatic crystals with a melting point in the range of 243-245°C (recrystallized from chloroform/ether), were formed.

NMR ($CDCl_3$) $\delta$ : 1.36 (t, 3H, J=[illegible]Hz), [illegible] 3H), 2.09 (dd, 1H, J=5.14Hz), [illegible] (q, 2H, J=8Hz), 2.70 (s, 3H), [illegible] 4.00 (s, 3H), 5.31 (s, 2H), [illegible] 7.36-7.72 (m, 3H), 7.97 (dd, 1H, J=[illegible] (dd, 1H, J=2.8Hz), 8.22 (dd, 1H, J=[illegible] (d, 1H, J=2Hz)

MS (m/e) : 566 ($M^+$-COEt-[illegible])

Application Example 9

Using the same method as in Application Example 2, from 150 mg (0.24 mmol) of compound 9, 85 mg (65.5%) of compound 10, in the form of brown acicular crystals with a melting point of >300°C (recrystallized from pyridine/chloroform/ether), were formed.

NMR(DMSO-$d_6$) $\delta$ : 1.16(s, 3H), 2.03(dd, 1H, J=5.14Hz), 2.17(s, 3H), 2.40(q, 2H, J=8Hz), 3.16-3.56(1H), 3.96(s, 3H), 5.08(s, 2H), 6.40 (br. s, 1H), 7.08-7.26(m, 1H), 7.30-7.68(m, 2H), 7.80-8.24(m, 4H), 8.66(s, 1H), 9.20(s, 1H), 10.04(s, 1H)

MS(m/e) : 539 (M+1)

Application Example 10

Using the same method as in Application Example 6, from 170 mg (0.3 mmol) of compound 1 and 240 mg (1.5 mmol) of n-butyric anhydride, 135 mg (71%) of compound 11, in the form of brown acicular crystals with a melting point in the range of 113-115°C (recrystallized from chloroform/ether), were formed.

NMR ($CDCl_3$) $\delta$ : 1.10(t, 3H, J=8Hz), 1.80(s, 3H), 1.72-2.04(m, 2H), 2.10(dd, 1H, J=5.14Hz), 2.24(s, 3H), 2.46(t, 2H, J=8Hz), 2.76(s, 3H), 3.97(dd, 1H, J=7.14Hz), 4.02(s, 3H), 5.36(s, 3H), 6.99(dd, 1H, J=5.7Hz), 7.36-7.76(m, 4H), 7.92-8.36(m, 3H), 8.92(s, 1H)

MS(m/e) : 637 (M+1)

Application Example 11

Using the same method as in Application Example 2, from 95 mg (0.15 mmol) of compound 11, 50 mg (80.6%) of compound 12, in the form of a brown powder with a melting point in the range of 294-296°C (recrystallized from chloroform), were formed.

NMR(DMSO-$d_6$) $\delta$ : 0.98(t, J=8Hz), 1.43-1.84 (m, 2H), 2.02(dd, 1H, J=5.7Hz), 2.36(t, 2H, J=8Hz), 3.63(dd, 1H, J=7.4Hz), 3.96(s, 3H), 5.06(s, 2H), 7.16 (dd, 1H, J=5.7Hz), 7.18-7.33(m, 2H), 7.93-8.20 (m, 4H), 8.64(s, 1H), 9.23(s, 1H), 11.24(s, 1H)

MS(m/e) : 553 (M+1)

Application Example 12

170 mg (0.3 mmol) of compound 1 were dissolved in 10 mL of chloroform, followed by the addition of 0.084 mL (0.6 mmol) of triethylamine and then 0.88 mL (1.5 mmol) of methyl isocyanate. The mixture was stirred at room temperature for 1 h. After 2 mL of methanol were added, the solvent was removed by distillation under reduced pressure, and the residue was triturated with methanol, forming 150 mg (80.2%) of compound (I-1-2e; X = $CO_2Me$, Y = OAc, $R^3$ = Ac, $R^{4b}$ = Me) in the form of a light yellow powder with a melting point of >300°C.

MS(m/e): 593 ($M^+$ - NHMe)

In the same way as in Application Example 2, 10 [sic; 100] mg (0.17 mmol) of compound 1 were used to form 89 mg (93.7%) of compound 13 in the form of a light yellow powder with a melting point of >300°C (recrystallized from methanol).

NMR ($CDCl_3$+DMSO-$d_6$) $\delta$ : 2.21(s, 3H), 2.28 (dd, 1H, J=5, 14Hz), 2.83(s, 3H), 4.05(s, 3H), 4.96(br. s, 2H), 6.93(dd, 1H, J=5, 7Hz), 7.28-7.64 (m, 3H), 7.84-8.04(m, 3H), 8.84(d, 1H, J=2Hz)

MS(m/e) : 509 ($M^+$-NHMe)

Application Example 13

Using the same method as in Application Example 12, 170 mg (0.3 mmol) of compound 1 were used to form 139 mg (73%) of compound (I-1-2e; X = $CO_2Me$, Y = OAc, $R^3$ = Ac, $R^{4b}$ = Et) in the form of a light yellow powder.

MS(m/e): 593 ($M^+$ - NHEt).

In the same way as in Application Example 2, 100 mg (0.16 mmol) of said compound were used to form 61 mg (69%) of compound 14 in the form of a light green powder with a melting point of >300°C (recrystallized from acetone/water).

NMR (CDCℓ$_3$+CD$_3$OD) δ : 1.16(t, 3H, J=7.5Hz), 2.08(s, 3H), 2.31(dd, 1H, J=5.14Hz), 3.04-3.28 (3H), 4.01(s, 3H), 4.15(d, 1H, J=17Hz), 4.67(d, 1H, J=17Hz), 6.80(dd, 1H, J=5.7Hz), 7.16-7.96 (m, 6H), 8.44(d, 1H, J=2Hz)

MS(m/e) : (M$^+$-NH$_2$Et)

Application Example 14

Using the same method as in Application Example 12, 170 mg (0.3 mmol) of compound 1 were used to form 172 mg (83.6% ) of compound (I-1-2e; X = $CO_2Me$, Y = OAc, $R^3$ = Ac, $R^{4b}$ = Ph) in the form of a light yellow powder with a melting point of >300°C.

MS (m/e): 593 ($M^+$ - NHPh)

Using the same method as in Application Example 2, 140 mg (0.2 mmol) of said compound were used to form 71 mg (59%) of compound 15 in the form of a light green powder with a melting point of >300°C.

NMR (CDCℓ$_3$+CD$_3$OD) δ : 2.16(s, 3H), 2.27(dd, 1H, J=5.14Hz), 3.20-3.52(m, 1H), 4.04(s, 3H), 4.67(d, 1H, J=18Hz), 4.90(d, 1H, J=18Hz), 6.80-8.04(m, 11H), 8.75(d, 1H, J=2Hz)

MS(m/e) : 508 (M$^+$-NH$_2$Ph)

Application Example 15

170 mg (0.3 mmol) of compound 1 were dissolved in a mixture of 10 mL of THF and 1 mL of acetic acid, followed by the addition of 1 mL of an aqueous solution of 120 mol (1.5 mmol) of potassium cyanate. The mixture was stirred at room temperature for 1 h. After the solvent was removed by distillation under reduced pressure, the residue was triturated with water, forming 178 mg (97.3%) of compound (I-1-2d; X = $CO_2Me$, Y = $CO_2Me$, Y = OAc, $R^3$ = Ac) in the form of a yellow powder with a melting point of >300°C.

MS (m/e): 593 ($M^+ - NH_2$)

In the same way as in Application Example 2, 80 mg (0.13 mmol) of said compound were used to form 34 mg (50%) of compound 16 in the form of a light yellow powder with a melting point of >300°C.

NMR(DMSO-$d_6$) $\delta$ : 2.11(dd, 1H, J=5.14Hz), 2.17 (s, 3H), 3.20-3.63(1H), 3.97(s, 3H), 5.79(br. s. 2H), 6.40(s, 1H), 6.97-7.23(m, 1H), 7.30-7.70 (m, 2H), 7.76-8.10(m, 4H), 8.70(s, 1H), 8.79(s. 1H), 9.20(s, 1H), 9.30(s, 1H)

MS(m/e) : 5 0 8 ($M^+$-$NH_2$)

Application Example 16

110 mg (0.2 mmol) of compound i (III-1; X = $CO_2Me$, Y = OAc, $R^3$ = Ac) were dissolved in 10 mL of dichloromethane. Under ice cooling, 133 mg (1 mmol) of aluminum chloride and 0.015 mL (0.2 mmol) were added, followed by stirring at the same temperature for 2 h. 10 mL of water were added, and the organic layer was extracted. Saturated saline was used for washing, followed by drying with anhydrous magnesium sulfate. The residue was refined by silica gel chromatography (chloroform), and was then recrystallized from chloroform/methanol, forming 60 mg (50.8%) of compound 17 in the form of colorless prismatic crystals with a melting point of >300°C. Also, 5 mg (4%) of compound 18, in the form of yellow prismatic crystals with a melting point of >300°C, were formed.

Compound 17:

NMR(CDCl$_3$) $\delta$ : 1.76(s, 3H), 1.09(dd, 1H, 5.14Hz), 2.28(s, 3H), 2.52(s, 3H), 2.69(s, 3H), 3.93(dd, 1H, J=7.14Hz), 4.01(s, 3H), 5.20(s, 3H), 6.89(dd, 1H, J=5.7Hz), 7.28-7.72(m, 3H), 7.88-8.24(m, 3H), 9.68(s, 1H)

MS(m/e) : 594 (M+1)

Compound 18:

NMR(CDCl$_3$) $\delta$ : 1.82(s, 3H), 2.21(dd, 1H, J=5.14Hz), 2.34(s, 3H), 2.75(s, 3H), 2.80(s, 3H), 2.82(s, 3H), 4.06(dd, 1H, J=7.14Hz), 4.07(s, 3H), 5.40(s, 2H), 7.03(dd, 1H, J=5.7Hz), 7.56(d, 1H, J=8Hz), 8.01(d, 1H, J=8Hz), 8.24(d, 1H, J=8Hz), 8.25(d, 1H, J=8Hz), 8.60(s, 1H), 9.84(d, 1H, J=2Hz)

MS(m/e) : 636 (M+1)

Application Example 17

330 mg (0.6 mmol) of compound i (III-1; X = $CO_2Me$, Y = OAc, $R^3$ = Ac) were dissolved in 30 mL of dichloromethane. Under ice cooling, 0.46 mL (4.2 mmol) of titanium tetrachloride and 0.11 mL (1.2 mmol) of dichloromethyl methyl ether were added, followed by stirring at room temperature for 3 h. 10 mL of water were added,

and the organic layer was extracted. Saturated saline was used for washing, followed by drying with anhydrous magnesium sulfate. After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (chloroform), and was then recrystallized from chloroform/methanol, forming 130 mg (37%) of compound 19 in the form of colorless prismatic crystals with a melting point of >300°C. Also, 130 mg (35.7%) of compound 20, in the form of brown powder with a melting point of >300°C, were formed.

Compound 19: NMR(DMSO-$d_6$) $\delta$ : 1.72(s, 3H), 2.04-2.36(m, 1H), 2.25(s, 3H), 2.68(s, 3H), 3.80-4.08(m, 1H), 4.00(s, 3H), 5.43(s, 2H), 7.20-8.40(m, 7H), 9.60(s, 1H), 10.16(s, 1H).
MS(m/e) : 580 (M+1)

Compound 20: NMR(DMSO-$d_6$) $\delta$ : 1.72(s, 3H), 2.09-2.16(m, 1H), 2.29(s, 3H), 2.56(s, 3H), 3.80-4.08(m, 1H), 4.00(s, 3H), 5.08-5.44(m, 2H), 7.28-7.48(m, 1H), 7.88-8.32(m, 4H), 8.56(s, 1H), 9.40(s, 1H), 10.04(s, 1H), 10.25(s, 1H)
MS(m/e) : 608 (M+1)

Application Example 18

Using the same method as that in Application Example 2, 50 mg (0.08 mmol) of compound 17 were used to form 30 mg (70%) of compound 21 in the form of colorless acicular crystals with a melting point of >300°C.

NMR(DMSO-$d_6$) $\delta$ : 2.08(dd, 1H, J=5.14Hz), 2.15 (s, 3H), 2.70(s, 3H), 3.43(dd, 1H, J=7.14Hz), 3.93(s, 3H), 5.01(d, 1H, J=18Hz), 5.07(d, 1H, J=18Hz), 6.39(s, 1H), 7.21(dd, 1H, J=5.7Hz), 7.38(t, 1H, J=7Hz), 7.51(t, 1H, J=7Hz), 7.95(d, 1H, J=8Hz), 8.01(d, 1H, J=8Hz), 8.08(d, 1H, J=8Hz), 8.10(d, 1H, J=7Hz), 8.69(s, 1H), 9.92(d, 1H, J=2Hz)

MS(m/e) : 509 ($M^+$)

Application Example 19

Using the same method as that in Application Example 2, 50 mg (0.086 mmol) of compound 19 were used to form 20 mg (46.8%) of compound 22 in the form of a colorless powder with a melting point of >300°C.

NMR(DMSO-$d_6$) $\delta$ : 2.00-2.08(m, 1H), 2.16(s, 3H), 3.12-3.60(m, 1H), 3.96(s, 3H), 5.08(br. s, 2H), 7.08-7.68(m, 3H), 7.84-8.28(m, 4H), 9.80(s, 1H), 10.16(s, 1H)

MS(m/e) : 495 ($M^+$)

Application Example 20

Using the same method as that in Application Example 2, 121 mg (0.2 mmol) of compound 20 were used to form 51 mg (49%) of compound 23 in the form of a colorless powder with a melting point of >300°C.

NMR(DMSO-$d_6$) $\delta$ : 2.06(dd, 1H, J=5.14Hz), 2.20
(s, 3H), 3.50(dd, 1H, J=7.14Hz), 3.96(s, 3H),
5.14(br. s, 2H), 6.56(s, 1H), 7.31(dd, 1H, J=5.7Hz),
7.92-8.24(m, 4H), 8.67(s, 1H), 8.84(br. s, 1H),
9.77(s, 1H), 10.13(s, 1H), 10.21(s, 1H)
MS(m/e) : 523 ($M^+$)

Application Example 21

20 mg (0.033 mmol) of compound 17 were dissolved in chloroform. Then, 25 mg (0.15 mmol) of m-chloroperbenzoic acid were added twice in 1 h, followed by heating with reflux for 3 h. After washing with a saturated aqueous solution of sodium bicarbonate and then with water, the sample was dried with anhydrous magnesium sulfate. After the solvent was removed by distillation under reduced pressure, it was refined by silica gel chromatography (chloroform) and then recrystallized from chloroform/ether, forming 10 mg (18.0%) of compound (I-1-4; X = $CO_2Me$, Y = OAc, $R^3$ = Ac, $R^{1b}$ = Me) in the form of a brown powder with a melting point of >300°C.

NMR ($CDCl_3$) δ : 1.79(s, 3H), 2.09(dd, 1H, J=5.14Hz), 2.26(s, 3H), 2.40(s, 3H), 2.70(s, 3H), 3.94(dd, 1H, J=7.14Hz), 4.00(s, 3H), 5.34(s, 2H), 6.98(dd, 1H, J=5.7Hz), 7.20-7.70(m, 3H), 7.92-8.20(m, 3H), 8.90(d, 1H, J=2Hz)

MS(m/e) : 610 (M+1)

Using the same method as in Application Example 2, 1.0 g (1.6 mmol) of said compound was used to form 0.3 [g] (38.8%) of compound 24 in the form of red-brown prismatic crystals with a melting point of >300°C (with recrystallization from chloroform).

NMR(DMSO-$d_6$) δ : 1.97(dd, 1H, J=5.14Hz), 2.12(s, 3H), 3.35(dd, 1H, J=7.14Hz), 3.92(s, 3H), 5.01(s, 2H), 6.32(s, 1H), 6.88-7.16(m, 2H), 7.28-7.64(m, 2H), 7.72(d, 1H, J=8Hz), 7.80-8.20(m, 2H), 8.60(s, 1H), 8.71(d, 1H, J=2Hz), 9.10(s, 1H)

MS(m/e) : 481 (M+1)

Application Example 22

Using the same method as in Application Example 21, 182 mg (0.3 mmol) of compound 20 were used to form 80 mg (42%) of compound (I-1-4; X = $CO_2Me$, Y = OAc, $R^3$ = Ac, $R^{1b}$ = H) in the form of a brown powder.

NMR ($CDCl_3$) $\delta$ : 1.84(s, 3H), 1.96-2.40(m, 1H), 2.28(s, 3H), 2.76(s, 3H), 3.84-4.12(m, 1H), 4.02(s, 3H), 5.36(s, 2H), 6.72-7.08(m, 1H), 7.24-7.64(m, 3H), 7.76-8.08(m, 2H), 8.48(s, 2H), 9.01(d, 1H, J=2Hz)

Using the same method as in Application Example 2, 80 mg (0.13 mmol) of said compound were used to form 10 mg (15%) of compound 25 in the form of a yellow powder with a melting point of >300°C.

NMR(DMSO-$d_6$) $\delta$ : 1.97(dd, 1H, J=5.14Hz), 2.10 (s, 3H), 3.00-3.50(1H), 3.92(s, 3H), 4.94(s, 2H), 6.23(s, 1H), 6.80-7.12(m, 3H), 7.35(d, 1H, J=2Hz), 7.65(d, 1H, J=8Hz), 7.76(d, 1H, J=8Hz), 8.46(s, 1H), 8.67(d, 1H, J=2Hz), 9.03(s, 1H), 9.20(s, 1H)

MS(m/e) : 500 (M+1)

Application Example 23

9.6 mg (0.2 mmol) of a 50% solution of sodium hydroxide were suspended in 1 mL of DMF. Under ice cooling, 2 mL of DMF solution of 96 mg (0.2 mmol) of compound 24 were added. After 20 min, 0.013 mL (0.2 mmol) of methyl iodide was added, followed by stirring for 1 h. After the reaction was complete, a saturated solution of ammonium chloride was added, followed by extraction with chloroform, washing by saturated saline and drying with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue was refined by

silica gel chromatography (chloroform) and was then recrystallized from dichloromethane/methanol, forming 45 mg (45.3%) of compound 26 in the form of brown acicular crystals with a melting point in the range of 293-294°C.

NMR ($CDCl_3$+DMSO-$d_6$) $\delta$ : 2.05(dd. 1H. J=5. 14Hz). 2.16(s. 3H). 3.00-3.50(1H). 3.92(s. 3H). 3.96 (s. 3H). 5.03(br. s. 2H). 6.96-8.12(m. 6H). 8.54 (br. s. 1H). 8.92(d. 1H. J=2Hz)

MS(m/e) : 4 9 8 (M+1)

Application Example 24

Using the same method as in Application Example 23, 96 mg (0.2 mmol) of compound 24 and ethyl iodide were used to form 75 mg (73.5%) of compound (27) in the form of yellow acicular crystals with a melting point in the range of 283-286°C (with recrystallization from chloroform).

NMR(DMSO-$d_6$) $\delta$ : 1.46(t. 3H. J=7Hz). 2.03(dd. 1H. J=5. 14Hz). 2.18(s. 3H). 3.96(s. 3H). 4.20(q. 2H. J=7Hz). 5.07(s. 2H). 6.36(s. 1H). 7.07-7.28 (m. 2H). 7.32-7.68(m. 2H). 7.80-8.20(m. 3H). 8.64(s. 1H). 8.91(d. 1H. J=2Hz)

MS(m/e) : 5 1 2 (M+1)

Application Example 25

Using the same method as in Application Example 23, 96 mg (0.2 mmol) of compound 24 and 1-iodopropane were used to form 60 mg (57.1%) of compound (28) in the form of yellow acicular crystals with a melting point in the range of 228-230°C (with recrystallization from chloroform).

NMR(DMSO-$d_6$) $\delta$ : 1.07(t, 3H, J=8Hz), 1.72-2.24 (m, 3H), 2.16(s, 3H), 2.90-3.40(1H), 3.94(s, 3H), 4.08(t, 2H, J=7Hz), 5.04(br. s, 2H), 6.34(s, 1H), 7.00-7.24(m, 2H), 7.32-7.60(m, 2H), 7.76-8.16 (m, 3H), 8.60(s, 1H), 8.87(d, 1H, J=2Hz)

MS(m/e) : 526 (M+1)

Application Example 26

Using the same method as in Application Example 23, 96 mg (0.2 mmol) of compound 24 and 2-iodopropane were used to form 40 mg (38%) of compound (29) in the form of yellow-brown prismatic crystals with a melting point in the range of 213-214.5°C (with recrystallization from chloroform).

NMR(DMSO-$d_6$) $\delta$ : 1.35(d, 6H, J=7Hz), 1.99(dd, 1H, J=5, 14Hz), 2.14(s, 3H), 3.00-3.52(1H), 3.92(s, 3H), 4.48-4.80(m, 1H), 5.02(br. s, 2H), 6.32(br. s, 1H), 7.00-7.24(m, 2H), 7.32-9.64(m, 2H), 7.72-8.20(m, 3H), 8.60(br. s, 1H), 8.87(d, 1H, J=2Hz)

Application Example 27

Using the same method as in Application Example 23, 96 mg (0.2 mmol) of compound 24 and 1-iodobutane were used to form 35 mg (32.5%) of compound (30) in the form of yellow-brown prismatic crystals with a melting point in the range of 166-168°C (with recrystallization carried out using chloroform).

NMR(DMSO-$d_6$) $\delta$ : 0.99(t, 3H, J=7Hz), 1.32-2.24 (m, 5H), 2.16(s, 3H), 3.16-3.52(1H), 3.93(s, 3H), 4.12(t, 2H, J=8Hz), 5.03(br. s, 2H), 6.33(s, 1H), 7.04-7.28(m, 2H), 7.28-7.68(m, 2H), 7.70-8.20 (m, 3H), 8.60(s, 1H), 8.89(d, 1H, J=2Hz)

MS(m/e) : 540 (M+1)

Application Example 28

2.51 g (4.3 mmol) of compound (19) were dissolved in a solvent mixture of 20 mL of methanol and 100 mL of chloroform. Under ice cooling, 488 mL (12.4 mmol) of sodium borohydride were added. After stirring at this temperature for 30 min, a 3N aqueous solution of hydrochloric acid was added to adjust the pH to 2. After extraction, the organic layer was washed sequentially with a saturated aqueous solution of sodium bicarbonate and saturated saline and then dried with anhydrous magnesium sulfate. The residue was triturated with ether, forming 1.8 g (72%) of compound 31 in the form of a light yellow powder with a melting point in the range of 270-277°C.

NMR ($CDCl_3$+$CD_3OD$) δ : 1.80(s, 3H), 2.11(dd, 1H, J=5.14Hz), 2.26(s, 3H), 2.64(s, 3H), 3.93 (dd, 1H, J=7.14Hz), 4.03(s, 3H), 4.86(s, 2H), 5.22(s, 2H), 6.99(dd, 1H, J=5.7Hz), 7.40-7.72 (m, 4H), 7.80-8.08(m, 2H), 9.04(s, 1H)

MS(m/e) : 581 ($M^+$)

Application Example 29

500 mg (0.86 mmol) of compound 31 were dissolved in 30 mL of chloroform, and then 0.64 mL (8.6 mmol) of ethanethiol and 199 mg (0.86 mmol) of camphorsulfonic acid were added. The mixture was stirred at room temperature for 2 h. Then, the mixture was washed sequentially with a saturated aqueous solution of sodium bicarbonate and saturated saline and then dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue was refined by silica gel chromatography (5% ethyl acetate/toluene), forming 340 mg (63%) of compound 32 in the form of colorless prismatic crystals with a melting point in the range of 181-184°C.

NMR ($CDCl_3$) δ : 1.28(t, 3H, J=8Hz), 1.76(s, 3H), 2.11(dd, 1H, J=5.14Hz), 2.26(s, 3H), 2.53 (q, 2H, J=8Hz), 2.80(s, 3H), 3.97(dd, 1H, J=7.14Hz), 4.00(s, 2H), 4.01(s, 3H), 5.36(s, 2H), 7.02(dd, 1H, J=5.7Hz), 7.14-7.80(m, 4H), 7.92-8.20(m, 2H), 9.13(s, 1H)

MS(m/e) : 626 ($M^+$)

Application Example 30

125 mg (0.2 mmol) of compound 32 were dissolved in ethyl acetate, and then 200 mg of Raney nickel were added. The mixture was heated with reflux for 7 h. After the reaction solvent was filtered through Celite, the solvent was removed by distillation under reduced pressure, forming 116 mg (100%) of compound 33 in the form of a light yellow powder.

NMR ($CDCl_3$) $\delta$ : 1.75(s, 3H), 2.04(dd, 1H, J=5.14Hz), 2.20(s, 3H), 2.48(s, 3H), 2.61(s, 3H), 3.86(dd, 1H, J=7.14Hz), 3.99(s, 3H), 5.08(s, 2H), 6.91(dd, 1H, J=5.7Hz), 7.16-7.64(m, 4H), 7.80-8.04(m, 2H), 8.80(s, 1H)

MS(m/e) : 566 ($M^+$)

Application Example 31

Using the same method as that in Application Example 2, 80 mg (0.12 mmol) of compound 32 were used to form 50 mg (77%) of compound 34 in the form of colorless prismatic crystals with a melting point of >300°C.

NMR ($CDCl_3$) $\delta$ : 1.30(t, 3H, J=8Hz), 2.12(s, 3H), 2.54(q, 2H, J=8Hz), 2.97(dd, 1H, J=5.14Hz), 3.63(dd, 1H, J=7.14Hz), 3.80(s, 2H), 4.08(s, 3H), 4.37(d, 1H, J=18Hz), 4.59(d, 1H, J=18Hz), 5.28(s, 1H), 5.56(s, 1H), 6.79(dd, 1H, J=5.7Hz), 7.12-7.70(m, 4H), 7.80-8.12(m, 2H), 8.60(s, 1H)

MS(m/e) : 540 ($M^+$-1)

Application Example 32

Using the same method as that in Application Example 2, 100 mg (0.17 mmol) of compound 33 were used to form 70 mg (82%) of compound 35 in the form of a light yellow powder with a melting point of >300°C.

NMR ($CDCl_3$) $\delta$ : 2.12(s, 3H), 2.38(s, 3H), 2.95(dd, 1H, J=5.14Hz), 3.48(dd, 1H, J=7.14Hz), 4.04(s, 3H), 4.24(d, 1H, J=18Hz), 2.48(d, 1H, J=18Hz), 5.42(s, 1H), 5.75(s, 1H), 6.78(dd, 1H, J=5.7Hz), 6.94-7.20(m, 2H), 7.28-7.62(m, 2H), 7.81(dd, 1H, J=2.8Hz), 8.00(d, 1H, J=8Hz), 8.40(s, 1H)

MS(m/e) ; 481 ($M^+$)

Application Example 33

90 mg (0.166 mmol) of compound 34 were dissolved in 5 mL of chloroform, and then 29 mL (0.166 mmol) of m-chloroperbenzoic acid were added. The mixture was stirred for 2 h at room temperature in the dark and then washed sequentially with a saturated aqueous solution of sodium bicarbonate and saturated saline and then dried with anhydrous magnesium sulfate. The residue was refined by silica gel chromatography (2% methanol/chloroform), forming 60 mg (65%) of compound 36 in the form of a light yellow powder with a melting point of >300°C.

NMR(DMSO-$d_6$) $\delta$ : 1.25(t, 3H, J=7Hz), 2.03(dd, 1H, J=5.14Hz), 2.15(s, 3H), 2.64-2.86(m, 2H), 3.36-3.41(m, 1H), 3.92(s, 3H), 4.11(d, 1H, J=13Hz), 4.28(d, 1H, J=13Hz), 4.97(d, 1H, J=18Hz), 5.03(d, 1H, J=18Hz), 7.13(dd, 1H, J=5.7Hz), 7.36(t, 1H, J=7Hz), 7.44(dd, 1H, J=1.8Hz), 7.48(d, t, 1H, J=1.8Hz), 7.90(d, 1H, J=8Hz), 7.94(d, 1H, J=8Hz), 8.62(s, 1H), 9.15(s, 1H)

MS(m/e) : 480 ($M^+$-S(O)Et)

Application Example 34

93 mg (0.2 mmol) of K-252 were dissolved in 3 mL of pyridine. Under ice cooling, 0.024 mL (0.48 mmol) of bromine was added, and the mixture was stirred overnight. After the reaction was complete, THF was added into the reaction solution, and the mixture was washed sequentially with a 5% aqueous solution of sodium thiosulfate and saturated saline. After it was dried with anhydrous magnesium sulfate, the solvent was removed by distillation under reduced pressure. The residue was recrystallized from THF and methanol, forming 70 mg (54%) of compound 37 in the form of a yellow-brown powder with a melting point of 251-252°C.

NMR($CDCl_3$—DMSO-$d_6$) $\delta$ : 1.96-2.30(m, 1H), 2.20(s, 3H), 3.12-3.60(m, 1H), 4.00(s, 3H), 5.04(s, 2H), 6.36(s, 1H), 7.04-7.24(m, 1H), 7.36-8.22(m, 6H), 8.64(br. s, 1H), 9.48(br. s, 1H)

MS(m/e) : 547 ($M^+$)

Application Example 35

300 mg (0.6 mmol) of compound d obtained in Reference Example 4 were dissolved in a solvent mixture of 90 mL of THF and 10 mL of water. Then, 0.32 mL (6 mmol) of methylhydrazine were added, followed by stirring at room temperature for 1 day. The mixture was washed with saturated saline and then dried with anhydrous magnesium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was refined by silica gel chromatography (1% methanol/chloroform), forming 126 mg (50%) of compound 38 in the form of a yellow-brown powder.

NMR(DMSO-$d_6$) $\delta$ : 1.92-2.36(1H). 2.03(s. 3H). 2.23(s. 3H). 3.08-3.60(1H). 3.12(s. 3H). 5.00 (s. 3H). 6.92-7.16(m. 1H). 7.20-7.60(m. 4H). 7.72-8.28(m. 3H). 9.24(d. 1H. J=8Hz)

MS(m/e) : 5 2 4 (M+1)

Application Example 36

300 mg (0.6 mmol) of compound d obtained in Reference Example 4 and 753 mg (6 mmol) of glycine methyl ester hydrochloride salt were dissolved in a solvent mixture of 90 mL of THF and 10 mL of water. Then, 0.84 mL of triethylamine was added, and the mixture was stirred at room temperature for 1 day. It was then washed with saturated saline. After the mixture was dried with anhydrous magnesium sulfate, the solvent was removed by distillation under reduced pressure. The residue was refined

by silica gel chromatography (1% methanol/chloroform), forming 87 mg (26%) of compound 39 in the form of a yellow-brown powder.

NMR ($CDCl_3$) $\delta$ : 1.72(s, 3H), 1.92-2.50(1H), 2.40(s, 3H), 3.68-4.52(m, 3H), 3.82(s, 3H), 5.02(br. s, 2H), 6.96-8.20(m, 8H), 9.31(d, 1H, J=8Hz)

MS(m/e) : 566 ($M^+$)

Application Example 37

Using the same method as that in Application Example 36, 500 mg (0.97 mmol) of compound d prepared in Reference Example 4 and 2.27 g (9.7 mmol) of L-proline benzyl ester hydrochloride salt were used to form 195 mg (29%) of compound 40 in the form of a colorless powder with a melting point in the range of 202-205°C.

NMR ($CDCl_3$) $\delta$ : 1.52(s, 3H), 1.80-2.50(m, 5H), 2.36(s, 3H), 3.08-3.52(m, 2H), 3.84-4.30(m, 2H), 4.64(s, 2H), 5.14(d, 1H, J=13Hz), 5.31(d, 1H, J=13Hz), 6.98(dd, 1H, J=5.14Hz), 7.16-7.60(m, 5H), 7.70-7.96(m, 2H), 9.32(d, 1H, J=8Hz)

MS(m/e) : 683 ($M^+$)

Application Example 38

132 mg (0.2 mmol) of compound 40 were dissolved in 5 mL of DMF, followed by the addition of 50 mg of 10% palladium/carbon. The mixture was stirred at 40°C in a hydrogen gas flow for 3.5 h. After the reaction solution was filtered through Celite, the solvent was removed by means of distillation under reduced pressure, and the residue was refined by silica gel chromatography (chloroform/methanol/28% aqeous ammonia of

90:10:0.5), forming 80 mg (67%) of compound 41 with a melting point of >300°C and in the form of a light yellow powder.

NMR(DMSO-$d_6$) $\delta$ : 1.66(s, 3H), 1.88-2.36(m, 5H), 2.49(s, 3H), 3.20-3.60(m, 2H), 3.95(dd, 1H, J=7.14 Hz), 4.12-4.50(m, 1H), 5.04(s, 2H), 7.00-7.70 (m, 5H), 7.86(dd, 1H, J=2.8Hz), 8.00-8.24(m, 2H), 8.61(s, 1H), 9.23(d, 1H, J=8Hz)

MS(m/e) : 593 (M+1)

Application Example 39

87 mg (0.15 mmol) of compound 39 were dissolved in 5 mL of THF, followed by the addition of 0.24 mL (0.68 mmol) of a 2N aqueous solution of sodium hydroxide. The mixture was stirred at room temperature for 2 h. After the pH was adjusted to 2 with a 3N aqueous solution of hydrochloric acid, the sample was washed with saturated saline and dried with anhydrous magnesium sulfate. After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (chloroform/methanol/28% aqeous ammonia, 90:10:5), forming 27 mg (35%) of compound 42 with a melting point of >300°C and in the form of colorless powder.

NMR(DMSO-$d_6$) $\delta$ : 1.96-2.36(m, 1H), 2.20(s, 3H),
3.08-3.50(1H), 3.88-4.04(m, 2H), 5.03(br. s, 2H),
6.53(s, 1H), 6.90-8.24(m, 6H), 8.52-8.80(m, 2H),
9.26(d, 1H, J=8Hz)
MS(m/e) : 511 (M+1)

Application Example 40

4.67 g (10 mmol) of K-252 were dissolved in 400 mL of THF, followed by the addition of 50 mL of a THF solution of 0.38 g (10 mmol) of lithium aluminum hydride at -20°C. The mixture was stirred at the same temperature for 1 h. After the pH was adjusted to 2 with a 3N aqueous solution of hydrochloric acid, the sample was filtered through Celite, and the filtrate was washed with saturated saline and dried with anhydrous magnesium sulfate. After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (chloroform), forming 1.56 g (35.7%) of compound 43 with a melting point of >300°C and in the form of a light yellow powder.

NMR ($CDCl_3$+DMSO-$d_6$) $\delta$ : 2.04-2.48(m, 1H),
2.24(s, 3H), 3.08-3.76(1H), 4.90(br. s, 2H),
6.91(dd, 1H, J=5.7Hz), 7.08-7.60(m, 5H), 7.76-
8.08(m, 2H), 9.19(d, 1H, J=8Hz), 10.10(s, 1H)
MS(m/e) : 437 ($M^+$)

Application Example 41

100 mg (0.23 mmol) of compound 43 were dissolved in 5 mL of THF and 0.5 mL of water, followed by addition of 79 mL (1.1 mmol) of hydroxylamine hydrochloride salt. The mixture was stirred for 1 day. After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (1% methanol/chloroform), forming 85 mg (82%) of compound 44 with a melting point in the range of 245-256°C and in the form of a light yellow powder.

NMR(DMSO-$d_6$) $\delta$ : 1.98-2.30(m, 1H). 2.20(s, 3H).
3.16-3.70(m, 1H). 5.03(s, 2H). 6.84-7.08(m, 1H).
7.16-8.20(m, 8H). 8.58(s, 1H). 9.26(d, 1H, J=8Hz)
MS(m/e) : 452 ($M^+$)

Application Example 42

Using the same method as in Application Example 41, 100 mg (0.23 mmol) of compound 43 and 128 mg (1.1 mmol) of semicarbazide hydrochloride were used to form 75 mg (66%) of compound 45 with a melting point of >300°C and in the form of a yellow-brown powder.

NMR(DMSO-$d_6$) $\delta$ : 1.90-2.36(1H). 2.08(s, 3H).
3.00-3.60(1H). 5.00(s, 2H). 6.96-8.20(m, 8H).
8.56(br. s, 1H). 9.22(d, 1H, J=8Hz)
MS(m/e) : 495 (M+1)

Application Example 43

Using the same method as in Application Example 41, 87 mg (0.2 mmol) of compound 43 and 264 mg (1.0 mmol) of aminoguanidine sulfate were used to form 60 mg (60%) of compound 46 with a melting point of >300°C and in the form of a light yellow powder.

NMR(DMSO-$d_6$) $\delta$ : 1.96-2.30(m, 1H), 2.15(s, 3H),
3.04-3.64(m, 1H), 5.02(br. s, 1H), 6.44(s, 1H),
7.00-8.20(m, 8H), 8.60(s, 1H), 9.22(d, 1H, J=8Hz)
MS(m/e) : 494 (M+1)

Application Example 44

Using the same method as in Application Example 41, 87 mg (0.2 mmol) of compound 43 and 181 mg (1.0 mmol) of 2-hydrazino-2-imidazoline hydrobromide were used to form 55 mg (53%) of compound 47 with a melting point of >300°C and in the form of a light yellow powder.

NMR(DMSO-$d_6$) $\delta$ : 1.68-2.30(m, 1H), 2.08(s, 3H),
3.00-3.70(1H), 5.00(s, 2H), 5.96(s, 1H),
7.00-8.12(m, 8H), 8.56(s, 1H), 9.21(d, 1H, J=8Hz)
MS(m/e) : 520 (M+1)

Application Example 45

Using the same method as in Application Example 23, 184 mg (0.4 mmol) of K-252 and butyl iodide were used to form 38 mg

(20%) of compound 48 with a melting point of 300-302°C and in the form of colorless prismatic crystals.

NMR ($CDCl_3$) δ : 2.23(dd, 1H, J=6.13Hz), 2.20 (s, 3H), 3.12(s, 3H), 3.28-3.48(m, 1H), 3.37(s, 3H), 4.04(s, 3H), 5.00(s, 2H), 7.03(dd, 1H, J=6.8 Hz), 7.28-7.64(m, 5H), 7.88-8.08(m, 2H), 9.46 (br, d, 1H, J=8Hz)

MS(m/e) : 495 ($M^+$)

Application Example 46

467 mg (1 mmol) of K-252 were dissolved in 20 mL of chloroform, followed by the addition of 133 mg (1 mmol) of N-chlorosuccinimide and 164 mg (1 mmol) of AIBN, and then heating with reflux for 3 h. After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (chloroform), forming 229 mg (46%) of compound 49 with a melting point in the range of 125-129°C and in the form of a light yellow powder.

NMR ($CDCl_3$) δ : 2.20(s, 3H), 2.68(dd, 1H, J= 5.14Hz), 3.43(dd, 1H, J=7.14Hz), 4.12(s, 3H), 4.88(d, 1H, J=15Hz), 5.04(d, 1H, J=15Hz), 6.87 (dd, 1H, J=5.7Hz), 7.24-7.64(m, 5H), 7.84-8.00 (m, 2H), 9.00(d, 1H, J=8Hz)

MS(m/e) : 501 ($M^+$)

Application Example 47

120 mg (0.27 mmol) of compound h prepared in Reference Example 8 were dissolved in 5 mL of DMF. Under ice cooling, 98 mg (0.55 mmol) of thiocarbonyldiimidazole were added, and the mixture was stirred for 1 h at the same temperature. After the reaction was complete, 30 mL of THF were added into the reaction solution, and the mixture was washed with saturated saline. After [the extract] was dried with anhydrous magnesium sulfate, the solvent was removed by distillation under reduced pressure, forming 120 mg (93%) of compound 50 in the form of a light yellow powder with a melting point >300°C.

NMR(DMSO-$d_6$) $\delta$ : 2.10-2.64(m, 1H), 2.32(s, 3H), 3.00-3.52(m, 1H), 4.05(d, 1H, J=11Hz), 4.38(d, 1H, J=11Hz), 5.02(s, 2H), 6.96-8.16(m, 7H), 8.60(s, 1H), 9.21(d, 1H, J=8Hz)

MS(m/e) : 481 (M+1)

Application Example 48

88 mg (0.18 mmol) of compound 50 were dissolved in 2 mL of DMF, followed by the addition of 0.1 mL of methyl iodide and then stirring at room temperature for 2.5 h. After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (chloroform), forming 14 mg (15.7%) of compound 51 with a melting point in the range of 223-225°C and in the form of a yellow powder.

NMR(DMSO-$d_6$) $\delta$ : 2.08-2.44(m, 1H). 2.24(s, 3H). 2.30(s, 3H). 3.20(dd, 1H, J=7.14Hz). 4.06(d, 1H, J=14Hz). 4.57(d, 1H, J=14Hz). 5.02(s, 2H). 7.12-8.20(m, 7H). 8.63(s, 1H). 9.24(d, 1H, J=8Hz)

MS(m/e) : 494 ($M^+$)

Application Example 49

87 mg (0.2 mmol) of compound e prepared in Reference Example 5 were dissolved in 5 mL of chloroform, followed by addition of 104 mg (1 mmol) of 2,2-dimethoxypropane and 10 mg of camphorsulfonic acid, and then heating with reflux for 2 h. The reaction solution was sequentially washed with saturated sodium bicarbonate and saturated saline and then dried with anhydrous magnesium sulfate. The residue was refined by silica gel chromatography (1% methanol/chloroform), forming 68 mg (71.5%) of compound 52 with a melting point in the range of 278-280°C and in the form of a yellow-brown powder.

NMR ($CDCl_3$) $\delta$ : 1.14(s, 3H). 1.40(s, 3H). 2.24(s, 3H). 2.41(dd, 1H, J=5.14Hz). 2.82(dd, 1H, J=5.14Hz). 4.05(d, 1H, J=10Hz). 4.49(d, 1H, J=10Hz). 4.96(s, 2H). 6.68(dd, 1H, J=5.7Hz). 7.24-8.20(m, 7H). 9.40-9.60(m, 1H)

MS(m/e) : 479 ($M^+$)

Application Example 50

467 mg (1 mmol) of K-252 were dissolved in 10 mL of acetonitrile, followed by the addition of 133 mg (1 mmol) of nitronium tetrafluoroborate and then stirring at room temperature for 3 h. After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (5% DMF/chloroform), forming 50 mg (10%) of compound 53 with a melting point of >300°C and in the form of a yellow powder.

NMR(DMSO-$d_6$) $\delta$ : 2.12(dd, 1H, J=5.14Hz), 2.16 (s, 3H), 3.45(dd, 1H, J=7.4.14Hz), 3.94(s, 3H), 4.99(d, 1H, 18Hz), 5.06(d, 1H, 18Hz), 6.44(s, 1H), 7.26(dd, 1H, J=5.7.4Hz), 7.39(t, 1H, J=8Hz), 7.53(t, 1H, 7Hz), 7.96(d, 1H, 8Hz), 8.08(t, 2H, J=8Hz), 8.31(dd, 1H, J=2.4.7Hz), 8.77(s, 1H), 10.09(d, 1H, J=2Hz)

MS(m/e) : 512 ($M^+$),

Application Example 51

93 mg (0.2 mmol) of K-252 were dissolved in 5 mL of THF, followed by the addition of 0.17 mL (2 mmol) of chlorosulfonyl isocyanate under ice cooling. The mixture was stirred at the same temperature for 2 h. Then, 1 mL of water was added, and the mixture was stirred at 70°C for 1 h. The reaction solution was then washed with a saturated aqueous solution of sodium bicarbonate and saturated saline and dried with anhydrous

magnesium sulfate. After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (2% methanol/chloroform), forming 85 mg (77%) of compound 54 with a melting point in the range of 280-285°C and in the form of a colorless powder.

NMR (DMSO-$d_6$) $\delta$ : 2.17 (dd, 1H, J=5.14Hz), 2.18 (s, 3H), 3.92 (dd, 1H, J=7.14Hz), 3.94 (s, 3H), 5.28 (d, 1H, 18Hz), 5.34 (d, 1H, 18Hz), 7.22 (dd, 1H, J=5.7Hz), 7.32 (t, 1H, J=7Hz), 7.42 (t, 1H, J=7Hz), 7.50~7.58 (m, 2H), 7.95~8.01 (m, 3H), 8.06 (d, 1H, J=8Hz)

MS (m/e) : 554 (M+1)

Application Example 52

43.9 mg (0.1 mmol) of compound e prepared in Reference Example 5 were dissolved in 1 mL of DMF, followed by the addition of 40 mg (0.1 mmol) of N-benzyloxycarbonylglycine anhydride and 0.016 mL (0.12 mmol) of triethylamine. Then, the mixture was stirred at 100°C for 1 h. The reaction solution was then washed with saturated saline and dried with anhydrous magnesium sulfate. After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (2% methanol/chloroform), forming 30 mg (48%) of compound 55.

NMR(CDCℓ$_3$) δ : 2.01(s, 3H), 2.80-3.40(m, 2H),
3.92-4.80(m, 6H), 5.04(s, 2H), 5.40-5.80(m, 3H),
6.50(m, 1H), 6.80-7.62(m, 10H), 7.76(d, 1H, J=8Hz),
7.98(d, 1H, J=8Hz), 8.56(d, 1H, J=8Hz)
MS(m/e) : 631 (M+1)$^+$

## Application Example 53

60 mg (0.095 mmol) of compound 55 were dissolved in 1 mL of DMF and 10 mL of ethanol. Then, 0.15 mL of 1N hydrochloric acid and 60 mg of 10% palladium/carbon were added, followed by stirring at 40°C in a hydrogen gas flow for 10 min. Then, the reaction solution was filtered through Celite, followed by the addition of 15 mL of water into the filtrate. Ethanol was removed by distillation under reduced pressure. The residue was dried, forming 23 mg (49%) of compound 56.

NMR(DMSO-$d_6$) δ : 2.00-2.40(m, 1H), 2.24(s, 3H),
3.00-3.60(m, 1H), 4.03(s, 2H), 4.61(m, 2H), 5.03
(br, s, 2H), 6.00(s, 1H), 7.00-8.16(m, 8H), 8.60
(br, s, 1H), 9.22(d, 1H, J=8Hz)
MS(m/e) : 491 (M+1)$^+$

## Application Example 54

439 mg (1 mmol) of compound e prepared in Reference Example 5 were dissolved in 20 mL of chloroform, followed by the addition

of 1.36 g (5 mmol) of tri-O-acetyl-D-glucal and 623 mg (3.5 mmol) of NBS. The mixture was then stirred at room temperature for 8 h in the dark. The reaction solution was then washed sequentially with 1N sodium thiosulfate and saturated saline and then dried with anhydrous magnesium sulfate. After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (1% methanol/chloroform), forming 360 mg (46%) of glycoside substance (XXI; Y = OH, $R_1 = R_2 = R_3 =$ H, $W_1 = A_c$).

MS (m/e): 790 $(M + 1)^+$, 792 $(M + 1)^+$

280 mg (0.35 mmol) of said glycoside substance were suspended in 20 mL of toluene, followed by the addition of 60 mg (0.35 mmol) of AIBN and 0.49 mL (175 mmol) of tributyltin hydride. The mixture was then stirred at 60°C for 1 h. Ethyl acetate was then added into the reaction solution, which was then washed with saturated saline and dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue was refined by silica gel chromatography (0.5% methanol/chloroform), forming 70 mg (28%) of compound 57.

NMR(DMSO-$d_6$) $\delta$ : 1.75-1.83(m, 1H), 1.95-1.99 (m, 1H), 2.00(s, 3H), 2.03(s, 3H), 2.04(s, 3H), 2.15(s, 3H), 2.40-2.44(m, 1H), 3.10(dd, 1H, J=7.5, 13.5Hz), 3.84(d, 1H, J=10Hz), 3.89-3.93(m, 1H), 4.07-4.11 (m, 2H), 4.19(d, 1H, J=10Hz), 4.26-4.30(m, 2H), 4.88-5.18 (m, 5H), 5.64(s, 1H), 7.00(dd, 1H, J=5.5, 7.5Hz), 7.25-7.49(m, 4H), 7.80(d, 1H, J=8.4Hz), 7.97(d, 1H, J=8.4Hz), 8.04 (d, 1H, J=7.7Hz), 8.6 (s, 1H), 9.19(d, 1H, J=8Hz)

MS(m/e) : 712 $(M+1)^+$

Application Example 55

50 mg (0.07 mmol) of compound 57 were dissolved in a solvent mixture of 2.5 mL of THF and 0.5 mL of methanol, followed by the addition of 0.35 mL of a 1N aqueous solution of sodium hydroxide. The mixture was then stirred at room temperature for 1 h. The reaction solution was then washed with saturated saline and dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue was refined by silica gel chromatography (10% methanol/chloroform), forming .8 mg (20%) of compound 58.

NMR(DMSO-$d_6$) $\delta$ : 1.46-1.54(m, 1H), 1.98(dd, 1H, J=5.14Hz), 2.10-2.20(m, 1H), 2.15(s, 3H), 3.02-3.21(m, 4H), 3.45-3.58(m, 1H), 3.75-3.82 (m, 2H), 4.21(d, 1H, J=10Hz), 4.54(t, 1H, J=6Hz), 4.70-4.73(m, 1H), 4.92(q, 1H, J=2.4Hz), 4.96 (d, 1H, J=18Hz), 5.03(d, 1H, J=18Hz), 6.99(dd, 1H, J=5.7Hz), 7.26(t, 1H, J=8Hz), 7.33(t, 1H, J=7.5Hz), 7.43-7.50(m, 2H), 7.81(d, 1H, J=8.4Hz), 7.96(d, 1H, J=8.4Hz), 8.04(d, 1H, J=7.5Hz), 8.57(s, 1H), 9.20(d, 1H, J=7.9Hz)

MS(m/e) : 586 (M+1)$^+$

Application Example 56

42.1 mg (0.1 mmol) of compound j prepared in Reference Example 10 were dissolved in 1 mL of DMF, followed by the addition of 32.7 mg (0.15 mmol) of ß-D-thioglucose sodium salt.

The mixture was then stirred at 50°C for 2 h. The solvent was removed by distillation under reduced pressure. The residue was refined by silica gel chromatography (chloroform/methanol/28% aqeous ammonia of 9/1/0.1), forming 38 mg (62%) of compound 59.

NMR(DMSO-$d_6$) $\delta$ : 2.01(dd, 1H, J=5, 13.6Hz), 2.16(s, 3H), 3.04-3.79(m, 9H), 4.46(d, 1H, J=9.5 Hz), 4.70(br. t, J=5.5Hz), 4.96(d, 1H, J=18Hz), 5.03(d, 1H, J=18Hz), 5.10(br. s, 1H), 5.31(d, 1H, J=5.3Hz), 5.63(s, 1H), 7.03(m, 1H), 7.27-7.49 (m, 4H), 7.83(d, 1H, J=8.4Hz), 7.99-8.05(m, 2H), 8.60(s, 1H), 9.19(d, 1H, J=7.9Hz)

MS(m/e) : 618 $(M+1)^+$

Application Example 57

467 mg (1 mmol) of K-252 were dissolved in 5 mL of chloroform, followed by the addition of 500 mg of molecular sieve 4Å and 0.14 mL (2 mmol) of chlorosulfonic acid under ice cooling. The mixture was then stirred at the same temperature for 3 h. After 2 mL of water were added into the reaction solution, the solvent was removed by distillation under reduced pressure. The residue was refined by silica gel chromatography (chloroform/methanol/28% aqeous ammonia of 80/20/5), forming 142 mg (26%) of compound 60.

NMR(DMSO-$d_6$+D$_2$O) $\delta$ : 2.01(dd, 1H, J=5.13Hz), 2.14(s, 3H), 3.14-3.60(m, 1H), 3.90(s, 3H), 4.98 (br. s, 2H), 7.00-8.12(m, 6H), 9.40(s, 1H)

MS(m/e) : 548 (M+1)$^+$

Application Example 58

110 mg (0.2 mmol) of compound 60 were blended with 83 mg (0.4 mmol) of phosphorus pentachloride and 0.19 mL (2 mmol) of phosphorus oxychloride, followed by heating with reflux for 1.5 h. After 10 mL of water and 10 mL of THF were added into the reaction solution, the organic layer was extracted and then washed with saturated saline and dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure, and the residue was refined by silica gel chromatography (0.1% methanol/chloroform), forming 50 mg of the sulfonyl chloride substance

(X; X = $CO_2Me$, Y = OH, $R^3$ + H)

It was dissolved in 2 mL of DMF, followed by the addition of 0.079 mL (0.5 mmol) of pyridine and 0.05 mL of N-methylpiperazine. The mixture was then stirred at room temperature for 2 h. The solvent was removed by distillation under reduced pressure. The residue was refined by silica gel

chromatography (2.5% methanol/chloroform), forming 10 mg (8%) of compound 61.

NMR(DMSO-$d_6$) $\delta$ : 2.07-2.18(m, 1H), 2.12(s, 3H), 2.15(s, 3H), 2.44(m, 4H), 2.96(m, 4H), 3.20-3.50 (m, 1H), 3.93(s, 3H), 5.02(d, 1H, J=18Hz), 5.08 (d, 1H, J=18Hz), 6.41(s, 1H), 7.25(dd, 1H, J=5.7Hz), 7.37-8.17(m, 7H), 8.69(s, 1H), 9.70(d, 1H, J=2Hz)

MS(m/e) : 630 (M+1)+

Application Example 59

48.3 mg (0.1 mmol) of compound 24 prepared in Application Example 21 were dissolved in 2 mL of THF, followed by the addition of 36 mg (0.16 mmol) of p-nitrophenyl chloroformate and 0.033 mL (0.24 mmol) of triethylamine. The mixture was then stirred at room temperature for 1 day. The reaction solution was washed with saturated saline and dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue was refined by silica gel chromatography (1% methanol/chloroform), forming 66 mg (100%) of compound 62.

NMR($CDCl_3$) $\delta$ : 2.00(s, 3H), 2.52(dd, 1H, J= 5.14Hz), 3.34(dd, 1H, J=7.14Hz), 4.00(s, 3H), 4.14(d, 1H, J=18Hz), 4.36(d, 1H, J=18Hz), 5.12(s, 1H), 6.68(dd, 1H, J=5.7Hz), 6.80-8.40(m, 7H), 8.64 (s, 1H), 9.68(br, s, 1H)

MS(m/e) : 649 (M+1)+

Application Example 60

60 mg (0.074 mmol) of compound 62 were dissolved in 2 mL of DMF, followed by the addition of 16.4 mg (0.088 mmol) of N-isopropyl-1-piperazineacetamide. The mixture was then stirred at room temperature for 1 h. 10 mL of THF were added into the reaction solution and was washed sequentially with a saturated aqueous solution of sodium bicarbonate and with saturated saline and then dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue was refined by silica gel chromatography (4% methanol/chloroform), forming 42 mg (82%) of compound 63.

NMR(CDCl$_3$) $\delta$ : 1.20(d, 6H, J=8Hz), 2.00(s, 3H), 2.40-2.80(m, 5H), 3.00(s, 2H), 3.25(dd, 1H, J=7.14 Hz), 3.68-4.16(m, 5H), 4.00(s, 3H), 4.29(d, 1H, J=18Hz), 4.53(d, 1H, J=18Hz), 5.36(br. s, 1H), 5.56 (s, 1H), 6.68(dd, 1H, J=5.7Hz), 6.80-8.04(m, 7H), 8.56(br. s, 1H)

MS(m/e) : 695 (M+1)$^+$

Application Example 61

245 mg (0.42 mmol) of compound 31 prepared in Application Example 28 were dissolved in 20 mL of chloroform, followed by the addition of 20 mL of ethanol and 98 mg (0.42 mmol) of camphorsulfonic acid. The mixture was then heated with reflux for 6 h. The solvent was removed by distillation under reduced pressure. 20 mL of chloroform were added into the residue, and

the mixture was then washed sequentially with a saturated aqueous solution of sodium bicarbonate and with saturated saline and then dried with anhydrous magnesium sulfate. After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (1% methanol/chloroform), forming 143 mg (56%) of compound 64.

NMR(CDCl$_3$) $\delta$ : 1.30(t, 3H, J=7.5Hz), 1.80(s, 3H), 2.13(dd, 1H, J=5.14Hz), 2.28(s, 3H), 2.80(s, 3H), 3.65(q, 2H, J=7.5Hz), 3.97(dd, 1H, J=7.14Hz), 4.90 (s, 3H), 4.76(s, 2H), 5.36(s, 2H), 7.03(dd, 1H, J= 5.7Hz), 7.36-7.80(m, 4H), 7.88-8.15(m, 2H), 9.16 (s, 1H)

MS(m/e) : 610 (M+1)$^+$

Application Example 62

Under the same conditions as in Application Example 2, 330 mg (0.55 mmol) of compound 65 were used to form 259 mg (90%) of compound 85.

NMR(DMSO-$d_6$) $\delta$ : 1.20(t, 3H, J=7.5Hz), 2.24 (dd, 1H, J=5.14Hz), 2.16(s, 3H), 3.20-3.72(m, 3H), 3.93(s, 3H), 4.63(s, 2H), 5.02(s, 2H), 6.33(s, 1H), 7.13(dd, 1H, J= 5.7Hz), 7.24-8.15(m, 5H), 8.57(s, 1H), 9.16(s, 1H)

MS(m/e) : 526 (M+1)$^+$

Application Example 63

239 mg (0.46 mmol) of compound 65 were dissolved in 8 mL of THF and 0.8 mL of water. Under ice cooling, 52 mL (1.38 mmol) of sodium borohydride were added. After stirring at the same temperature for 2 h, the reaction solution was washed with saturated saline and dried with anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure. The residue was treated by THF-ether to form a powder. As a result, 152 mg (66%) of compound 66 were obtained.

NMR(DMSO-$d_6$) $\delta$ : 1.20(t, 3H), 1.98(dd, 1H, J=5.14Hz), 2.16(s, 3H), 3.18(dd, 1H, J=7.14Hz), 3.57(q, 2H, J=8Hz), 3.85(m, 2H), 4.64(s, 2H), 5.02(s, 2H), 5.14(m, 1H), 5.40(s, 1H), 7.00(dd, 1H, J=5.7 Hz), 7.24-7.60(m, 3H), 7.77(d, 1H, J=8Hz), 7.92-8.16(m, 2H), 8.56(s, 1H), 9.17(s, 1H)

MS(m/e) : 497 ($M^+$)

Reference Example 1

1 mL of thionyl chloride was added into a suspension prepared by adding 227 mg (0.5 mmol) of compound KT5556 (IIa) to 20 mL in ethanol, which was then heated under reflux. 1 mL of thionyl chloride was added after 2 h and after 4 h, respectively. Heating with reflux was carried out for a total time of 8 h. After the volatile substances in the reaction mixture were removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (chloroform/methanol),

forming 160 mg (66%) of compound a in the form of a light yellow powder.

Melting point: 193-195°C (acetone/methanol)

NMR(DMSO-$d_6$) $\delta$ : 9.22(d, 1H, J=7.6Hz). 8.1-7.85(m, 3H). 7.55-7.25(m, 4H). 7.11(dd, 1H, J=4.9, 7.3Hz). 5.04(d, 1H, J=17.7Hz). 4.98(d, 1H, J=17.7Hz). 4.40(m, 2H). 3.38(dd, 1H, J=7.3, 13.9Hz). 2.17(s, 3H). 2.02(dd, 1H, J=4.9, 13.9Hz). 1.43(t, 3H, J=7.1Hz)

MS(m/e): 481 ($M^+$)

IR(KBr) 3430, 1730, 1675, 1635, 1590, 1460, 745 $cm^{-1}$

Reference Example 2

2 mL of a solution of 184 mg (0.4 mmol) of K-252 in DMF were cooled by ice, and 19.2 mg (0.4 mmol) of 50% sodium hydride in mineral oil were added into it. After 20 min, 25 $\mu$L (0.4 mmol) of methyl iodide were added, followed by stirring for 1 h. 20 mL of chloroform were added into the reaction mixture. The solution was washed with water and then dried with anhydrous sodium sulfate. After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (chloroform), forming 65 mg (34%) of compound b in the form of a light yellow powder.

Melting point: 250-252°C (recrystallization dichloromethane/methanol)

NMR(CDCℓ$_3$) δ : 9.42(d, 1H, J=8Hz), 8.1-7.85 (m, 2H), 7.7-7.2(m, 5H), 7.03(dd, 1H, J=5.7 Hz), 5.08(s, 2H), 4.05(s, 3H), 3.37(dd, 1H, J=7, 14Hz), 3.13(s, 3H), 2.21(s, 3H), ca. 2.20(dd, 1H)

MS(m/e): 481 ($M^+$)

Reference Example 3

1.42 mL (15 mmol) of acetic anhydride were added into 50 mL of a solution of 4.53 g (10 mmol) of compound (IIa) in anhydrous pyridine, followed by stirring at room temperature for 1 h. After the solvent in the reaction mixture was removed by distillation under reduced pressure, 50 mL of 1N hydrochloric acid were added, and the mixture was stirred. The insoluble substances were filtered and washed with 1N hydrochloric acid and then with water. After drying under reduced pressure, 4.79 g (97%) of compound c, in the form of a light yellow powder, were obtained.

Melting point: 267-270°C

NMR(DMSO-$d_6$+CDCℓ$_3$) δ : 9.36(d, 1H, J=8Hz), 8.2-7.7(m, 3H), 7.7-7.25(m, 4H), 7.27(dd, 1H, J=5.7Hz), 5.07(S, 2H), 3.98(dd, 1H, J=7.14Hz), 2.35 (S, 3H), 2.12(dd, 1H, J=5.14Hz), 1.72(S, 3H)

IR(KBr) 3430, 1750, 1680, 1640, 1590, 1460, 1235, 745 $cm^{-1}$

Reference Example 4

60 mL of a solution of 2.5 g of compound c in thionyl chloride were heated under reflux for 2 h. The thionyl chloride was removed from the reaction solution by distillation under reduced pressure. 40 mL of ethyl ether were added to the solid residue, and the mixture was stirred. The insoluble substances were filtered and extracted with ethyl ether. After drying under reduced pressure, 2.29 g (88%) of compound d, in the form of a light yellow powder, were obtained.

Reference Example 5

100 mL of a solution of 7.01 g (15 mmol) of K-252 in anhydrous THF were cooled by ice, and 1.14 g (30 mmol) of lithium aluminum hydride were added into it, followed by stirring at room temperature for 2 h. After methanol was added and the excess reducing agent was decomposed, the reaction mixture was filtered through Celite. The filtrate was then washed with 1N hydrochloric acid and saturated saline and was then dried with anhydrous sodium sulfate. After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (chloroform/methanol), forming 5.34 g (81%) of compound c in the form of a light yellow powder.

Melting point: 266-275°C (recrystallization from methanol)

NMR(DMSO-$d_6$+CDC $\ell_3$) $\delta$ : 9.24 (d, 1H, J=8Hz), 8.2-7.7(m, 3H), 7.6-7.0(m, 4H), 6.74(dd, 1H, J=5.7Hz), 4.90(d, 1H, J=18Hz), 4.69(d, 1H, J=18Hz), 4.13(d, 1H, J=11Hz), 3.91(d, 1H, J=11Hz), 3.29 (dd , 1H, J=7.14Hz), 2.38(dd, 1H, J=5.14Hz), 2.19 (s, 3H)

MS(m/e): 440 ($M^+$+1)

Reference Example 6

2.70 g (14.2 mmol) of p-toluenesulfonyl chloride, 1.97 mL (14.2 mmol) of triethylamine, and 0.69 g (5.7 mmol) of N,N-dimethylaminopyridine were added into 30 mL of a solution of 2.49 g (5.7 mmol) of compound e in anhydrous THF. The mixture was stirred at room temperature overnight. 100 mL of THF were added into the reaction mixture, and the solution was washed using acid/alkali. After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (chloroform/methanol), forming 1.11 g (33%) of compound f in the form of a a light yellow powder.

Melting point: 207-210°C

NMR(DMSO-$d_6$+COC $\ell_3$) $\delta$ : 9.24 (d, 1H, J=8Hz), 8.15-7.8(m, 3H), 7.65-7.2(m, 4H), 6.62(dd, 1H, J=5.7Hz), 4.95(d, 1H, J=10Hz), 4.80(d, 1H, J=10Hz), 4.45(S, 2H), 3.05(dd, 1H, J=7.14Hz), 2.55(S, 3H), 2.36(dd, 1H, J=5.14Hz), 2.12(S, 3H)

MS(m/e): 422 [$M^+$−167 (OTs)]

| 元素分析値 ① | C | H | N |
|---|---|---|---|
| 推定値 (% ②) | 66.77 | 4.59 | 7.08 |
| 実測値 (% ③) | 66.74 | 4.45 | 7.26 |

IR(KBr) 3430, 1670, 1640, 1595, 1460, 1175, 745$cm^{-1}$

Key: 1 Results of elemental analysis
2 Estimated value
3 Measured value

Reference Example 7

A mixture of 594 mg (1.0 mmol) of compound f and 6 mL of a solution of 130 mg (2.0 mmol) of sodium azide in DMF was stirred at room temperature overnight. 50 mL of THF were added into the reaction mixture, and the solution was washed using acid/alkali. After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (chloroform/methanol), forming 405 mg (87%) of compound g in the form of a light yellow powder.

Melting point: 218-223°C (THF methanol)

NMR(DMSO-$d_6$+$CDCl_3$) $\delta$ : 9.31 (d, 1H, J=8Hz), 8.15-7.2(m, 7H), 6.87(dd, 1H, J=5.7Hz), 5.00(s, 2H), 3.99(d, 1 H, J=13Hz), 3.56(d, 1H, J=13Hz), 3.21(dd 1H, J=7.14Hz), 2.37(dd, 1H, J=5.14Hz), 2.19(s, 3H)

MS(m/e) : 465 ($M^+$+1)

IR(KBr) 3430, 2100, 1670, 1640, 1590, 1460, 745$cm^{-1}$

Reference Example 8

114 mg (3.0 mmol) of lithium aluminum hydride were added into 7 mL of a solution of 232 mg (0.5 mmol) of compound g in anhydrous THF, and the mixture was stirred at room temperature for 2 h. 30 mL of THF were added into the reaction mixture, and the solution was filtered through Celite. The filtrate was washed using acid/alkali. After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (chloroform/methanol), forming 68 mg (31%) of compound h in the form of a light yellow powder.

Melting point: >300°C (methanol)

NMR(DMSO-$d_6$+CDC$\ell_3$) $\delta$ : 9.21 (d, 1H, J=7.9Hz),
8.1-7.7(m, 3H), 7.55-7.25(m, 4H), 7.00(dd, 1H,
J=5.2, 7.4Hz), 5.04(d, 1H, J=17.5Hz), 4.97 (d,
1H, J=17.5Hz), 3.25(dd, 1H, J=7.4, 13.6Hz),
3.13(d, 1H, J=12.9Hz), 2.88(d, 1H, J=12.9Hz),
2.12(s, 3H), 1.91(dd, 1H, J=5.2, 13.6Hz)
MS(m/e) : 439 ($M^+$+1)
IR(KBr) 3440, 1665, 1640, 1590, 745$cm^{-1}$

Reference Example 9

2 g (4.2 mmol) of K-252 were dissolved into 10 mL of THF and 4 mL of acetic anyhydride and 2.6 g of dimethylaminopyridine were added into the mixture, then stirred at room temperature overnight. The reaction solution was then washed in sequence with a 2% aqueous solution of hydrochloric acid and a saturated aqueous solution of sodium chloride, and was dried with anhydrous magnesium sulfate. After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (chloroform), forming 2.12 g (94%) of compound i in the form of a light yellow powder.

NMR(CDCℓ$_3$) δ : 1.76(s, 3H), 2.03(dd, 1H, J=5.14Hz), 2.16(s, 3H), 2.56(s, 3H), 3.86(dd, 1H, J=7.14Hz), 3.98(s, 3H), 5.07(s, 2H), 6.93(dd, 1H, J=5.7Hz), 7.14-7.66(m, 5H), 7.80-8.00(m, 2H), 9.02(d, 1H, J=8Hz)

Reference Example 10

228 mg (5.8 mmol) of 60% sodium hydride in mineral oil were added into 50 mL of a solution of 1,700 mg (2.9 mmol) of compound f obtained in Reference Example 6 in anhydrous THF under ice cooling, and the mixture was stirred at room temperature for 2.5 h. The reaction solution was then washed with acid/alkali. After the solvent was removed by distillation under reduced pressure, the residue was refined by silica gel chromatography (chloroform/methanol), forming 884 mg (73%) of compound j in the form of a light yellow powder.

Melting point: 292-296°C (decomposition)

NMR(DMSO-d$_6$) δ : 9.31 (d, 1H, J=7.5Hz), 8.1-7.75(m, 3H), 7.55-7.3(m, 4H), 7.22(dd, 1H, J=1.0, 6.0Hz), 5.00(s, 2H), 約3.35 (dd, 1H), 3.29(d, 1H, J=4.4Hz), 3.03(d, 1H, J=4.4Hz), 2.46(s, 3H), 2.00(dd, 1H, J=1.0, 14.7Hz)

MS(m/e) : 421 (M$^+$)

Reference Example 11

A 10% solution of hydroxypropylcellulose was blended with a mixture of 100 g of compound 44, 40 g of lactose, 18 g of corn starch and 10 g of carboxymethylcellulose calcium. The blend was pelletized using an extruding pelletizer having a 1.0-mm screen, followed by drying at 60°C. The dried pellets were screened through a 16-mesh sieve. Magnesium stearate was added into the portion passed through the sieve, forming the pellets. Then, the conventional method was used to form tablets containing 100 mg of compound 44 per tablet (170 mg) with 8 mm diameter.

Experimental Example 1

The activity of typical compound (I) in inhibiting C-kinase was measured using the method developed by T. Nishizuka (J. Biol. Chem., Vol. 257, p. 13341 (1982)). By varying the concentration of the test compound, the concentration of the compound for 50% inhibition of the enzyme activity ($IC_{50}$) was derived, with results listed in Table III.

Table III. C-kinase inhibition of the synthesized compounds.

| 化合物No.(1) | $IC_{50}$ μg/ml |
|---|---|
| 3 | 0.175 |
| 4 | 0.02 |
| 22 | 0.006 |
| 24 | 0.009 |
| 25 | 0.005 |
| 35 | 0.056 |
| 46 | 0.021 |
| 47 | 0.031 |
| 49 | 0.034 |
| 50 | 0.017 |
| 57 | 0.45 |
| 61 | 9 |
| K-252 (2) (参考化合物) | 0.016 |

Key: 1 Compound No.
2 (Reference compound)

Experimental Example 2

The histamine-inhibiting effects of typical compounds (I) were studied as follows.

Rats with a substance weight in the range of 150-180 g were killed by exsanquination under ether anesthesia. Then, 6 mL/animal of mast cell medium prepared according to the method of Sullivan et al. (J. Immunol., Vol. 114, p. 1473 (1975)

(referred to as MCM, with a composition of 150 mM NaCl, 3.7 mM KCl, 3 mM $Na_2HPO_4$, 3.5 mM $KH_2PO_4$, 1 mM $CaCl_2$, 5.6 mM glucose, 0.1% bovine serum albumin, and 10 U/mL of heparin) was injected into the abdomen. After 2 min of massage for the abdominal region, the abdomen was opened, and the exudate was extracted from the abdomen. The exudate extracted from 6 rats was subjected to centrifugal isolation at 4°C and 100 g for 5 min. An appropriate amount of MCM cooled in ice water was added to the sediment for washing three times. A peritoneal exudate cell (referred to as PEC hereinafter) sample was prepared appropriately to ensure that the final mast cell number was about $3 \times 10^4$ cells/mL. The mast cells were determined by dyeing the intracellular particles with 0.05% toluidine blue. 1 mL of the PEC sample prepared in this way was preincubated at 37°C for 10 min, followed by adding 0.1 mL of the test sample solution at one of various concentrations. After 10 min of incubation, 0.1 mL of 100 μg/mL phosphatidyl-L-serine and 0.1 mL of 1,000 μg/mL concanavalin were added, followed by incubation for 15 min. 3 mL of ice-cooled physiological saline were added to stop the reaction, followed by centrifugal isolation at 4°C and 1,100 g for 10 min, forming supernatant and sediment. The histamine content of the supernatant and sediment were measured using the method of Komatsu (Allergy, Vol. 27, p. 67 (1978)) with the aid of fluorescence. The histamine liberation rate is defined as the percent of the histamine content in the supernatant with respect to the total amount of histamine in the cells. Also, the following formula was used to calculate the test sample's inhibition of the histamine liberation rate.

Liberation inhibition rate (%) = (1 - (daily amount of histamine liberated in the presence of the drug)/(daily amount of histamine liberated in absence of the drug)) x 100

By varying the concentration of the test compound, the concentration of the compound corresponding to 50% inhibition of histamine liberated ($IC_{50}$) was derived, with results listed in Table IV.

Table IV. Effects of typical compounds (I) on inhibition of histamine liberation.

| 化合物No. (1) | $IC_{50}$, ng/ml |
|---|---|
| 49 | 12 |
| 24 | 20 |
| 44 | 16 |
| 50 | 17 |

Key: 1 Compound No.

Experimental Example 3

For the compounds prepared in this invention, cell growth inhibition was evaluated as follows. The results are listed in Table V.

(1) Test of MCF7 cell growth inhibition

MCF cells were prepared by incubation in a RPMI1640 culture containing 10% bovine fetal serum, 10 μg/mL insulin and $10^{-8}$M estradiol until cell concentration reached 4.5 x $10^4$ cells/mL. 0.1 mL of the MCF7 cells prepared in this way was loaded in each well of a 96 well microtiter plate. Then, 0.5 mL of test sample diluted appropriately with the culture solution after cultuing at 37°C in a carbon dioxide incubator was added to each well. After exposure for 72 h with incubation of the cells in a carbon dioxide incubator, the supernatant was removed, and PBS(-) was used for washing one time. Then, with 0.1 mL of fresh culture medium in each well, incubation was carried out at 37°C for 72 h in the carbon dioxide incubator. After removal of the supernatant, 0.1 mL of the culture solution containing 0.02% neutral red was added to each well, followed by 1 h of incubation in the carbon dioxide incubator at 37°. After the supernatant was removed, [the residue] was washed once with physiological saline. After the stain was extracted using 0.001N hydrochloric acid/30% ethanol, the absorption at 550 nm was measured using a microplate reader. By comparing the the absorption of the unprocessed cells and that of the cells processed with the drug at a known concentration, the drug concentration corresponding to 50% inhibition of the growth of the cells was calculated. It is denoted as $IC_{50}$.

(2) Test of HeLa $S_3$ cell growth inhibition

HeLa S3 cells were prepared by incubation in an MEM culture containing 10% bovine fetal serum and 2 mM glutamine until cell concentration reached 3 x $10^4$ cells/mL. 0.1 mL of the $HeLaS_3$ cells prepared in this way were added to each well of a 96 well microtiter plate.

The operation was then carried out in the same way as in (1).

(3) Test of COLO320DM cell growth inhibition

COLO320DM cells were prepared by incubation in a RPMI 1640 culture medium containing 10% bovine fetal serum, 100 U/mL penicillin and 100 $\mu$g/mL streptomycin until cell concentration reached $10^5$ cells/mL. 0.1 mL of the COLO320DM cells prepared in this way were added to each well of a 96 well microtiter plate. Then, the operation was carried out in the same way as in (1). The cells were counted with using a micro cell counter. By comparing the number of unprocessed cells to the number of cells processed with the drug at a known concentration, the drug concentration corresponding to 50% inhibition of the growth of the cells was calculated. It is denoted as $IC_{50}$.

Table V. Cell growth inhibition activities of synthesized compounds.

| 化合物番号 (1) | $IC_{50}$ (μg/ml) MCF7 | HeLaS$_3$ | COLO320DM |
|---|---|---|---|
| 3 | 0.13 | 0.01 | 0.05 |
| 4 | 0.95 | 0.07 | 0.10 |
| 24 | | 0.48 | |
| 25 | 0.84 | 0.44 | |
| 47 | 0.50 | 0.23 | 1.0 |
| 50 | | 0.28 | |
| 57 | 1.22 | 0.54 | 1.58 |
| 61 | 5.96 | 3.89 | |
| K-252 (2) (参考化合物) | 0.51 | 0.2 | 0.27 |

Key: 1 Compound No.
2 Reference compound

Effects of the invention

According to this invention, compound (I) and its pharmacologically tolerable salts inhibit C-kinase, liberation antihistamine, and platelet coagulation, exhibit anti-inflammatory activity and inhibit cell growth. Consequently, they are expected to find use as the active ingredients in antiallergic, antithrombotic, anti-inflammatory, and antineoplastic agents.

# JAPANESE PATENT OFFICE

# PATENT ABSTRACTS OF JAPAN

## 63295588

DERIVATIVE OF PHYSIOLOGICALLY ACTIVE SUBSTANCE K-252

Patent Number: JP63295588
Publication date: 1988-12-01
Inventor(s): HIRATA TADASHI; others: 01
Applicant(s):: KYOWA HAKKO KOGYO CO LTD
Application Number: JP19870327858 19871224
Priority Number(s):
IPC Classification: C07D498/18
EC Classification:

Abstract

NEW MATERIAL: A compound expressed by formula I (R<1> and R<2> are H, methyl, nitro, etc.; R<3> is H, Cl, lower alkanoyl, etc.; X is hydroxymethyl, formyl, carboxyl, etc.; Y is OH, lower alkanoyloxy, carbamoyloxy, etc., provided that at least one of R<1>-R<3> is a group other than H when X is hydroxymethyl, carboxyl, etc.) and salt thereof.
USE:An antiallergic agent, antithrombotic agent, anti-inflammatory agent, antitumor agent, etc., having powerful inhibitory activity against C-kinase.

PREPARATION: A raw material compound expressed by formula II, such as a physiologically active substance K-252, is reacted with a nitrating agent (e.g. nitronium tetrafluoroborate) in an amount of 1-1.1 equiv. based on the above- mentioned compound in an inert solvent, such as sulfolane, at room temperature - 80 deg.C for 1-2hr to afford the aimed compound expressed by formula I (R<1> or R<2> or both are nitro).

⑲日本国特許庁（JP）　⑪特許出願公開

⑫公開特許公報（A）　昭63－295588

⑤1Int.Cl.⁴　識別記号　庁内整理番号　⑬公開　昭和63年(1988)12月1日
C 07 D 498/18　8615－4C※

審査請求　未請求　発明の数 1　（全40頁）

⑤4発明の名称　生理活性物質K－252の誘導体

⑳特　願　昭62－327858
㉒出　願　昭62(1987)12月24日
優先権主張　㉜昭62(1987)1月22日㉝日本(JP)㉛特願　昭62－12719

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最終頁に続く

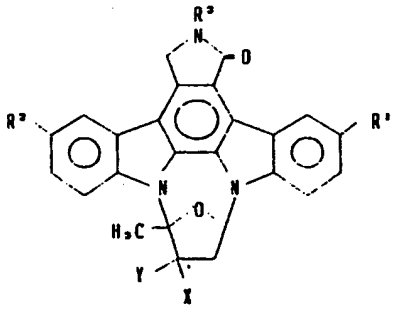
明　細　書

1．発明の名称

生理活性物質K－252の誘導体

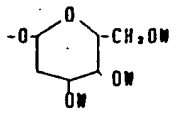
2．特許請求の範囲

式



（式中、$R^1$および$R^2$は同一または異なって、水素、メチル、ヒドロキシメチル、低級アルコキシメチル、低級アルキルチオメチル、低級アルキルスルフィニルメチル、ニトロ、ブロム、低級アルカノイル、ヒドロキシ、低級アルカノイロキシ、低級アルコキシ、$-NR^6R^7$（式中、$R^6$および$R^7$は一方が水素で他方が水素、低級アルカノイル、カルバモイル、低級アルキルアミノカルボニルまたはフェニルアミノカルボニルであるか、両者とも低級アルキルである）、スルホン酸、$-SO_3NR^6R^7$（式中、$R^6$および$R^7$は同一または異なって水素、低級アルキルまたは隣接する窒素原子と共に複素環を形成する基である）、$-OCOOR^8$（式中、$R^8$は低級アルキルまたは置換もしくは非置換のフェニルである）または$-OCONR^6R^7$（式中、$R^6$および$R^7$は前記と同義である）を表わし、$R^3$は水素、塩素、低級アルカノイル、カルバモイルまたは低級アルキルを表わし、Xはヒドロキシメチル、ホルミル、カルボキシル、低級アルコキシカルボニル、低級アルキルヒドラジノカルボニル、$-CH=N-R^9$〔式中、$R^9$はヒドロキシ、カルバモイルアミノ、$-NR^6R^7$（式中、$R^6$および$R^7$は前記と同義である）、グアニジノまたは2－イミダゾリルアミノである〕、$-CONHR^{10}$（式中、$R^{10}$はα－アミノ酸のアミノ基を除く残基であって、該アミノ酸のカルボキシル基は低級アルキルまたはベンジルでエステル化されていてもよい）、$-CH_2OCOR^{11}$（式中、$R^{11}$はα

一アミノ酸のカルボキシル基を除く残基であって、該アミノ酸のアミノ基はベンジルオキシカルボニルまたはt－ブトキシカルボニルで保護されていてもよい）または$-CH_2Z$ | 式中、Zは

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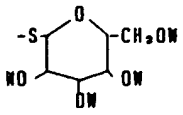



（式中、Wは水素、メチル、エチル、ベンジル、アセチルまたはトリフルオロアセチルである）で表わされる糖残基である | を表わし、Yはヒドロキシ、低級アルカノイロキシ、カルバモイルオキシまたは低級アルコキシを表わし、またはXとYが一体となって－Y－X－として$-O-C(CH_3)_2-O-CH_2-$，


$-OCNHCH_2-$ または

（式中、R''は低級アルキルである）である。

ただし、Xがヒドロキシメチル、カルボキシルまたは低級アルコキシカルボニルの場合、R'、R²およびR³の内少なくとも1つは水素以外の基である）で表わされるK－252誘導体およびその薬理的に許容される塩。

3．発明の詳細な説明

産業上の利用分野

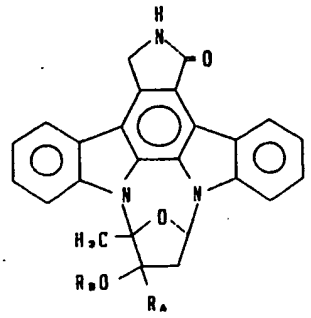
本発明はプロテインキナーゼC（以下C－キナーゼという）を阻害し、種々な薬理作用を有する新規化合物に関する。

従来の技術

C－キナーゼはフォスファチジドおよびカルシウムに依存して活性化されるタンパク質リン酸化酵素であり、広く生体内の組織や臓器に分布している。近年、本酵素は多くのホルモンや神経伝達物質などの細胞膜受容伝達機構において、極めて重要な役割を果たしていることが知られるようになった。そのようなC－キナーゼが関与する情報伝達機構により惹起される生理的反応の例として、血小板におけるセロトニン放出、リソゾーム酵素遊離および凝集反応、好中球のスーパーオキシド生成やリソゾーム酵素の遊離、副腎髄質からのエピネフリン遊離、腎糸球体からのアルドステロン分泌、ランゲルハンス島からのインシュリン分泌、マスト細胞からのヒスタミン遊離、回腸からのアセチルコリン遊離、血管平滑筋の収縮等が報告されている。さらに、C－キナーゼは細胞増殖や発ガン機構にも関与していると考えられている〔参考文献：Y. Nishizuka, Science, 225, 1365 (1984); H. Rasmussen ea al., Advance in Cyclic Nucleotide and Protein Phosphorylation Research, Vol. 18, P159, edited by P. Greengard and G. A. Robison, Raven Press, New York, 1984〕。このようにC－キナーゼは生体内の多くの重要な生理反応や各種病態に係わることが明らかになってきた。従って、C－キナーゼ活性をその特異的阻害剤等を用いることにより人為的に抑制することができれば、広く循環器系の疾病や、炎症、アレルギー、腫瘍などの予防、治療が可能になると考えられる。

一方、トリフルオペラジン、クロロプロマジン等の抗精神病薬剤、局所麻酔薬として知られるジベナミンやテトラカイン、あるいはカルモジュリン阻害剤W－7〔N－（6－aminohexyl）－5－chloro－1－naphthalenesulfonamide〕等の薬剤にC－キナーゼの抑制活性があることが見出されているが、いずれもそのC－キナーゼ抑制作用は各薬剤の主作用ではなく特異性は低く、また抑制活性も低い〔Y. Nishizuka et al., J. Biol. Chem., 255, 8378 (1980); R. C. Schatzman et al., Biochem. Biophys. Res. Commun., 98, 669 (1981); B. C. Wise et al., J. Biol. Chem., 257, 8489 (1982)〕。

一方、次式で表されるK－252，KT－5556およびR₁、R₂部位を修飾したK－252誘導体が知られている（K－252について特開昭60-41489，米国特許第455402号、KT－5556について特開昭61-176531、K－252誘導体について特開昭62-155284、同62-155285）。

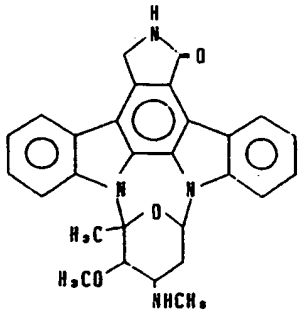


K－２５２：$R_A$＝$CO_2CH_3$，$R_B$＝H

ＫＴ－5556：$R_A$＝$CO_2H$，$R_B$＝H

特開昭60－41489にはＫ－２５２が抗ヒスタミン遊離作用、抗アレルギー作用を有することが、特開昭62-155284、同62-155285にはＫ－２５２誘導体がＣ－キナーゼ抑制活性および抗ヒスタミン遊離作用を有することが記載されている。また、特開昭61－176531にはＫＴ－5556が抗ヒスタミン遊離作用を有することが記載されている。また、Ｋ－２５２、ＫＴ－5556と同一化合物と推定される化合物が抗菌物質として報告されている〔M. Senzaki et al., J. Antibiotics, 38, 1437(1985)〕。この文献には上式で$R_A$＝$CO_2CH_3$，$R_B$＝$COCH_3$の化合物も開示されている。このＫ－２５２と同一化合物と推定される化合物およびそのハロゲン誘導体が特開昭62-120388、同62-164626に、また$R_A$を修飾した誘導体が特開昭62-240689に、いずれも血圧降下作用および利尿作用を有することが記載されている。

さらにＫ－２５２の構造に比較的近い構造を有する化合物として以下の構造を有し、抗菌作用を有するスタウロスポリン(Staurosporine)が知られている〔S. Omura et al., J. Antibiotics, 30, 275 (1977); A. Furusaki et al., J. Chem. Soc. Chem. Commun., 800 (1981); 特開昭60-185719〕。



Staurosporine

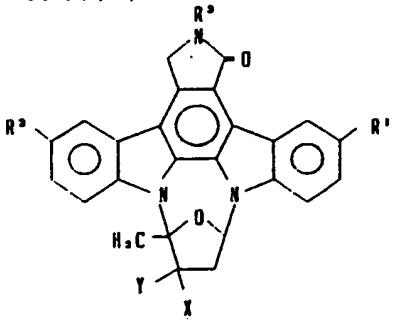
発明が解決しようとする問題点

強いＣ－キナーゼ阻害活性を有し抗アレルギー剤、抗血栓剤、抗炎症剤にあるいは抗腫瘍剤等の新しい活性成分は常に求められている。

問題点を解決するための手段

本発明によれば式（Ｉ）で表わされるＫ－２５２の新規な誘導体および薬理的に許容されるその塩が提供される。

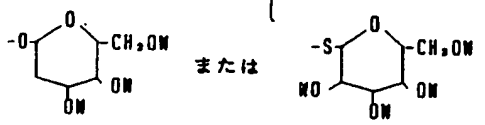
式（Ｉ）；



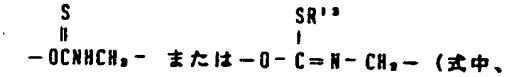
（Ｉ）

〔式中、$R^1$および$R^2$は同一または異なって、水素、メチル、ヒドロキシメチル、低級アルコキシメチル、低級アルキルチオメチル、低級アルキルスルフィニルメチル、ニトロ、ブロム、低級アルカノイル、ヒドロキシ、低級アルカノイロキシ、低級アルコキシ、$-NR^4R^5$（式中、$R^4$および$R^5$は一方が水素で他方が水素、低級アルカノイル、カルバモイル、低級アルキルアミノカルボニルまたはフェニルアミノカルボニルであるか、両者とも低級アルキルである）、スルホン酸、$-SO_2NR^6R^7$（式中、$R^6$および$R^7$は同一または異なって水素、低級アルキルまたは隣接する窒素原子と共に複素環を形成する基である）、$-OCOOR^8$（式中、$R^8$は低級アルキルまたは置換もしくは非置換のフェニルである）または$-OCONR^6R^7$（式中、$R^6$および$R^7$は前記と同義である）を表わし、$R^3$は水素、塩素、低級アルカノイル、カルバモイルまたは低級アルキルを表わし、Ｘはヒドロキシメチル、ホルミル、カルボキシル、低級アルコキシカルボニル、低級アルキルヒドラジノカルボニル、$-CH=N-R^9$〔式中、$R^9$はヒドロキシ、カルバモイルアミノ、$-NR^6R^7$（式中、$R^6$および$R^7$は前記と同義である）、グアニジノまたは２－イミダゾリルアミノである〕、$-CONHR^{10}$（式中、$R^{10}$はα－アミノ酸のアミノ

基を除く残基であって、該アミノ酸のカルボキシル基は低級アルキルまたはベンジルでエステル化されていてもよい）、$-CH_2OCOR''$（式中、R''はα－アミノ酸のカルボキシル基を除く残基であって、該アミノ酸のアミノ基はベンジルオキシカルボニルまたはt－ブトキシカルボニルで保護されていてもよい）または$-CH_2Z$ 式中、Zは



（式中、Wは水素、メチル、エチル、ベンジル、アセチルまたはトリフルオロアセチルである）で表わされる糖残基である を表わし、Yはヒドロキシ、低級アルカノイロキシ、カルバモイルオキシまたは低級アルコキシを表わし、またはXとYが一体となって－Y－X－として$-O-C(CH_3)_2-O-CH_2-$、



（式中、R''は低級アルキルである）である。

ただし、Xがヒドロキシメチル、カルボキシルまたは低級アルコキシカルボニルの場合、$R^1$、$R^2$および$R^3$の内少なくとも1つは水素以外の基である）。

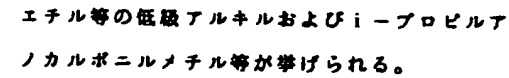
以下、式（I）で表わされる化合物を化合物（I）という。他の式番号の化合物についても同様である。化合物（I）は優れたC－キナーゼ抑制活性を有すると共に、優れた抗ヒスタミン遊離抑制活性、血小板凝集抑制活性、抗炎症活性あるいは細胞生育阻害活性も併有する。

式（I）中の各基の定義中、低級アルコキシメチル、低級アルキルチオメチル、低級アルキルスルフィニルメチル、低級アルコキシ、低級アルキルアミノカルボニル、低級アルキル、低級アルコキシカルボニルおよび低級アルキルヒドラジノカルボニルにいう低級アルキルは炭素数1～4の直鎖もしくは分岐のアルキル、例えばメチル、エチル、n－プロピル、i－プロピル、t－ブチル、n－ブチル等を包含する。各基の定義中、低級アルカノイルおよび低級アルカノイロキシにいう低級アルカノイルは炭素数1～4の直鎖もしくは分岐のアルカノイル、すなわちホルミル、アセチル、プロピオニル、n－ブチリルおよびi－ブチリル等を包含する。各基の定義中、形成される複素環としては、ピロリジン、ピペリジン、N－置換ピペラジン、モルホリンおよびN－置換ホモピペラジン等が包含され、該置換基としては、メチル、エチル等の低級アルキルおよびi－プロピルアミノカルボニルメチル等が挙げられる。

$R^6$の定義中、置換フェニルの置換基としては、低級アルキル、低級アルコキシ、ニトロおよびハロゲン等を包含する。ここで低級アルキルおよび低級アルコキシは上記と同義であり、ハロゲンはフッ素、塩素、臭素、ヨウ素である。

また、R''およびR''の定義中、α－アミノ酸はグリシン、アラニン、バリン、プロリン等を包含し、L体でもD体でもラセミ体でもよい。該アミノ酸の低級アルキルエステルにいう低級アルキルも上記と同様のものを包含する。

化合物（I）が酸性化合物である場合には塩基付加塩、塩基性化合物の場合には酸付加塩を形成させることができる。この場合酸性はXがα－アミノ酸残基を含む場合のカルボキシ等、塩基性は$R^1$中のアミノ、（ジ）低級アルキルアミノ、X中の$-CH=N-R^6$（$R^6=OH$の場合を除く）、およびα－アミノ酸残基を含む場合のアミノ－Y－X－中の



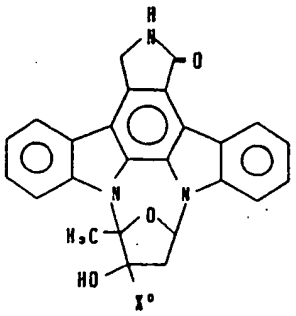
等によってもたらされる。化合物（I）の塩基付加塩としてはアンモニウム塩、リチウム、ナトリウム、カリウム塩のようなアルカリ金属塩、カルシウム、マグネシウム塩のようなアルカリ土類金属塩、トリエチルアミン、モルホリン、ピペリジン、ジシクロヘキシルアミン等の有機塩基との塩、およびアルギニン、リジン等の塩基性アミノ酸との塩があげられる。化合物（I）の酸付加塩としては塩酸塩、臭化水素酸塩、硫酸塩、硝酸塩、ギ酸塩、酢酸塩、安息香酸塩、マレイン酸塩、フマル酸塩、コハク酸塩、酒石酸塩、クエン酸塩、シュウ酸塩、メタンスルホン酸

塩、トルエンスルホン酸塩、アスパラギン酸塩、グルタミン酸塩等があげられる。非毒性の薬理的に許容される塩、例えば上記に列挙の塩基付加塩、酸付加塩が好ましいが、生成物の単離、精製にあたってはその他の塩もまた有用である。

本発明による化合物は、光学活性であるK－252等より、通常立体保持の反応で得られるものであるが、全ての可能な立体異性体およびそれらの混合物も本発明に包含される。

次に化合物（I）の製造方法について説明する。しかし、化合物（I）の製造方法は、それらに限定されるものではない。

化合物（I）は、K－252およびこれより導かれる次の式（IIa，b）



（II）

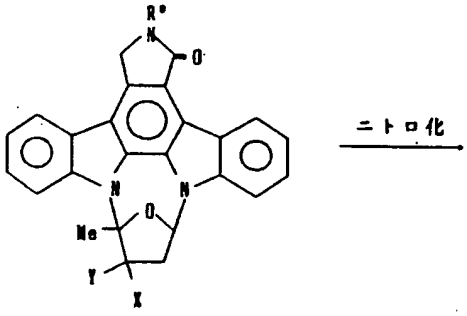
（IIa）（X° ＝COOH）

（IIb）（X° ＝CH₂OH）

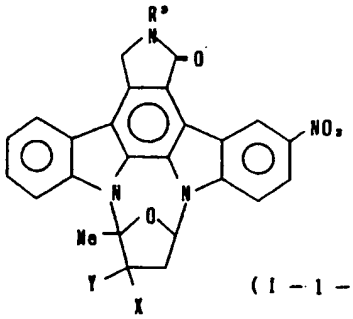
で表わされる化合物より種々の合成手段により製造される。なお、化合物（IIa）は特開昭61-176531に、化合物（IIb）は特開昭62-155285(参考例5参照）にそれぞれ開示されている。

なお、以下に示した製造方法において、定義した基が実施方法の条件下変化するかまたは方法を実施するのに不適切な場合、有機合成化学で常用される方法、例えば官能基の保護、脱保護等の手段〔例えば、プロテクティブ・グループス・イン・オーガニック・シンセシス、グリーン著、ジョン・ウィリー・アンド・サンズ・インコーポレイテッド（1981年）参照〕に付すことにより容易に実施することができる（例えば実施例2等参照）。

なお、以下に記載する構造式、表等における Me、Et、Pr、Bu、Ph、Ac、Bzℓ、CbzおよびTsはそれぞれメチル、エチル、プロピル、ブチル、フェニル、アセチル、ベンジル、ベンジルオキシカルボニルおよびトルエンスルホニルの基を意味する。



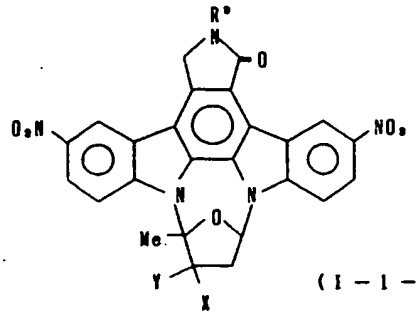
ニトロ化



（I－1－1）

方法1：R¹ および／またはR² に官能基を有する化合物（I－1）の合成

1－1：R¹ および／またはR² がニトロの化合物（I－1－1）および／または（I－1－1'）



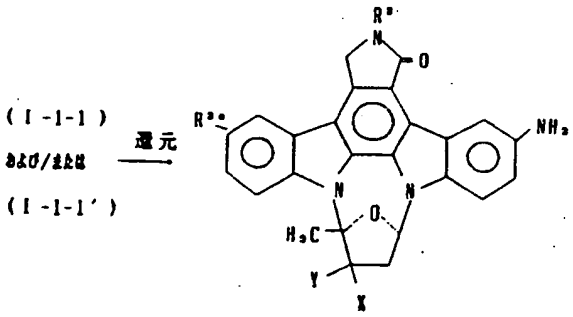
(I－1－1′)

(式中、X、YおよびR³は前記と同義である)

反応は化合物(III－1)〔化合物(I)において、R¹およびR²が水素である化合物および化合物(II)〕と適当なニトロ化剤、例えばテトラフルオロホウ酸ニトロニウムとを反応に不活性な溶媒中反応させることにより化合物(I－1－1)および/または(I－1－1′)を得る。ニトロ化剤は化合物(III－1)に対し通常1～1.1当量用いる。不活性溶媒はスルホラン、アセトニトリル、クロロホルム等を包含する。反応は室温～80℃で行い、通常1～2時間で終了する。

1－2：R¹および/またはR²が-NR⁴R⁵の化合物(I－1－2)

1－2a：R⁴およびR⁵が水素の化合物(I－1－2a)および/または(I－1－2a′)



(I-1-1)および/または(I-1-1′) —還元→

(I-1-2a)(R⁴⁴=H)

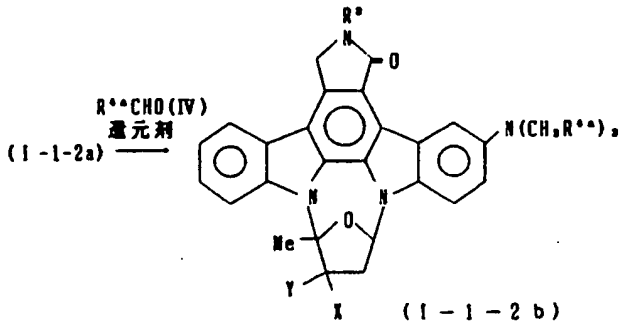
(I-1-2a′)(R⁴⁴=NH₂)

(式中、X、YおよびR³は前記と同義であり、R⁴⁴は水素またはアミノである)

ニトロ体(I－1－1)および/または(I－1－1′)を反応に不活性な溶媒中適当な還元法、例えば接触還元法により還元することにより化合物(I－1－2a)および/または(I－1－2a′)を得る。触媒は5～10%パラジウム/炭素等を包含し、通常化合物(I－1－1a)の重量に対し0.1～0.5倍重量用いる。不活性溶媒はテトラヒドロフラン(THF)、ジメチルホルムアミド(DMF)等を包含する。反応は通常室温で行い、1時間～1日で終了する。

なお、以下の方法1の説明において、2置換体(R¹＝R²≠H)の製法については特に記載しない場合もあるが、上記したと同様の1置換体の製法と同様の条件が適用しうる。

1－2b：R⁴およびR⁵がアルキルの化合物(I－1－2b)



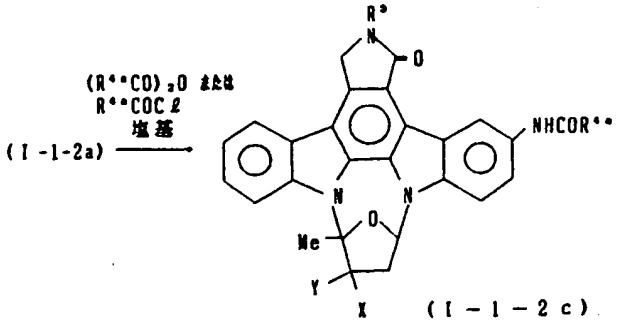
R⁴⁴CHO(IV) 還元剤 (I-1-2a) →

(I－1－2b)

(式中、X、YおよびR³は前記と同義であり、R⁴⁴は水素または低級アルキルを表わす)

アミノ体(I－1－2a)、アルデヒド体(IV)および適当な還元剤、例えばシアノ水素化ホウ素ナトリウムを反応に不活性な溶媒中反応させることにより化合物(I－1－2b)を得る。化合物(I－1－2a)に対し、通常化合物(IV)は大過剰、還元剤は1～2当量用いる。不活性溶媒としてはTHFと適当な低級アルカノール、例えばメタノールの1対1の混合溶媒等が用いられる。反応は通常室温で行い、0.5～1時間で終了する。

1－2c：R⁴(またはR⁵)がアルカノイルの化合物(I－1－2c)



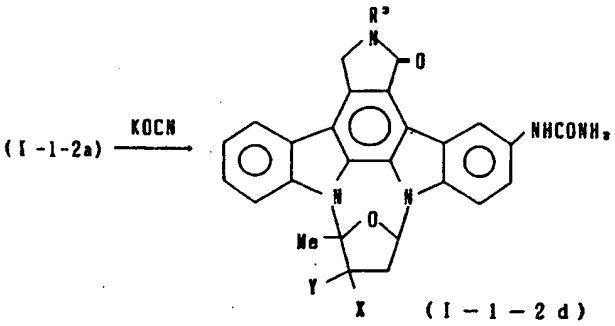
(R⁴⁴CO)₂O または R⁴⁴COCl 塩基 (I-1-2a) →

(I－1－2c)

（式中、X，Y，R³およびR⁴⁰は前記と同義である）

アミノ体（I－1－2a）とアシル化剤〔$(R^{40}CO)_2O$ または$R^{40}COCl$等〕とを塩基存在下で反応させることにより化合物（I－1－2c）を製造する。塩基はピリジン、トリエチルアミン等を包含する。アシル化剤は化合物（I－1－2a）に対し通常5～10当量使用する。反応は通常ピリジンを溶媒とし、室温下、1～6時間で終了する。

1－2d：R⁴（またはR⁵）がカルバモイルの化合物（I－1－2d）

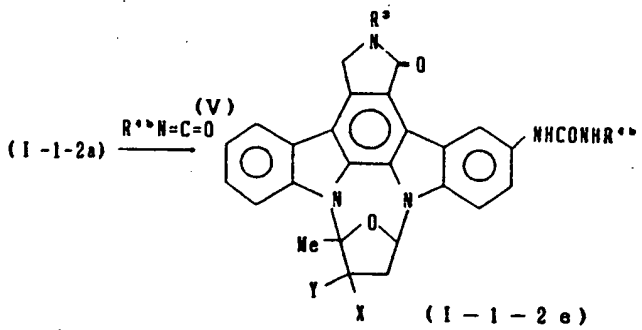



（I－1－2d）

（式中、X，YおよびR³は前記と同義である）

アミノ体（I－1－2a）と通常5当量程度のシアン酸カリウムとをTHF，酢酸および水（10：1：1）の混合溶媒中反応させることにより化合物（I－1－2d）を得る。反応は通常室温で行い、1時間程度で終了する。

1－2e：R⁴（またはR⁵）がアルキルアミノカルボニルまたはフェニルアミノカルボニルの化合物（I－1－2e）



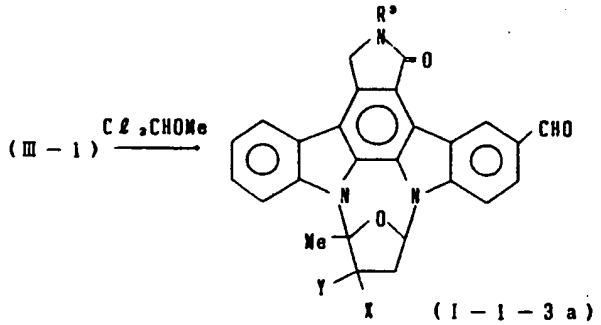

（I－1－2e）

（式中、X，YおよびR³は前記と同義でありR⁴⁰は低級アルキルまたはフェニルを表わす）

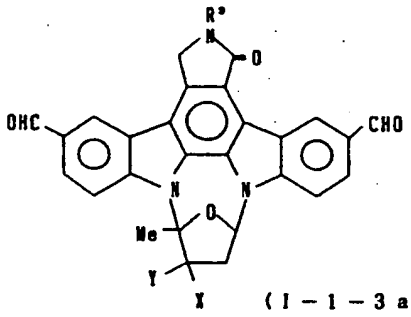
アミノ体（I－1－2a）とイソシアネート類（V）とを反応に不活性な溶媒中必要ならば塩基の存在下反応させることにより化合物（I－1－2e）を得る。塩基はトリエチルアミン等を包含する。化合物（I－1－2a）に対し通常化合物（V）は2～3当量、塩基は1～2当量用いる。不活性溶媒はジクロロメタン、クロロホルム等を包含する。反応は通常室温で行い、1～5時間で終了する。

1－3：R⁴および／またはR⁵がアルカノイルの化合物（I－1－3）

1－3a：アルカノイルがホルミルの化合物（I－1－3a）および／または（I－1－3a′）




（I－1－3a）

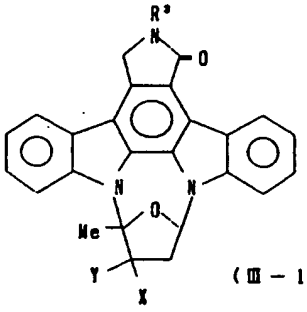



（I－1－3a′）

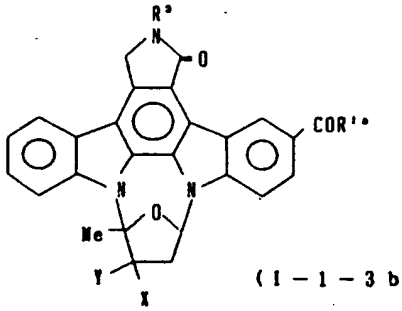
（式中、X，YおよびR³は前記と同義である）

化合物（Ⅲ－1）とジクロロメチルメチルエーテルとを反応に不活性な溶媒中適当なルイス酸、例えば四塩化チタンの存在下反応させることにより化合物（I－1－3a）および／または（I－1－3a′）を得る。化合物（Ⅲ－1）に対し通常ジクロロメチルメチルエーテルは1～2当量、四塩化チタンは5～7当量使用する。不活性溶媒としては通常ジクロロメタンを使用する。反応は通常室温下で行い1～12時間で終了する。

1－3b：アルカノイルがホルミル以外の化合物（I－1－3b）および／または（I－1－3b′）

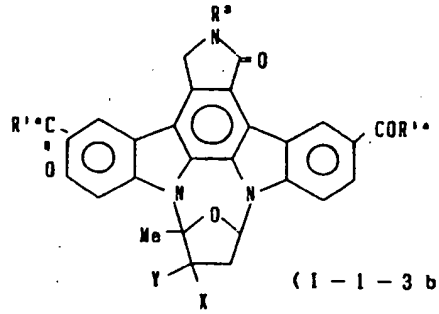



（III－1）




（I－1－3b）

＋

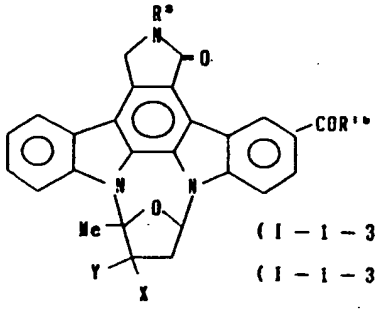



（I－1－3b′）

（式中、X，YおよびR³は前記と同義であり、R'⁰は低級アルキルを表わす）

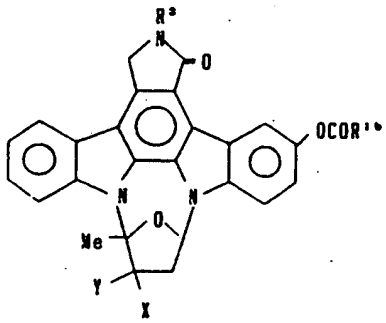
化合物（III－1）と酸クロリド（VI）とを反応に不活性な溶媒中適当なルイス酸、例えば塩化アルミニウムの存在下反応させて化合物（I－1－3b）および／または（I－1－3b′）を得る。化合物（III－1）に対し、通常化合物（VI）は1当量、ルイス酸は5当量用いる。不活性溶媒はジクロロメタン、クロロホルム等を包含する。反応は通常氷冷下で行い、1～12時間で終了する。

1－4：R¹およびR³がアルカノイロキシの化合物（I－1－4）




（I－1－3a）または（I－1－3b）

m－クロル過安息香酸



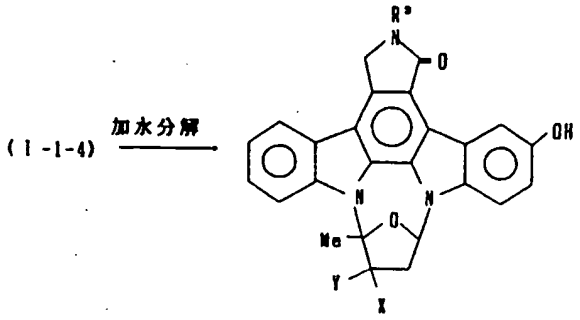

（I－1－4）

（式中、X，YおよびR³は前記と同義であり、R'⁰は水素または低級アルキルである）

アルカノイル体（I－1－3a）または（I－1－3b）と適当な酸化剤、例えばm－クロル過安息香酸とを反応に不活性な溶媒、通常クロロホルム中反応させて化合物（I－1－4）を得る。酸化剤は化合物（I－1－3a）または（I－1－3b）に対し通常5当量を1時間おきに2度用いる。反応は通常加熱還流下に行い、2～12時間で終了する。

また上記反応式に対応して、2置換アルカノイル体（I－1－3a′）または（I－1－3b′）から同様な条件で対応する2置換アルカノイロキシ体（I－1－4′）を得る。

1－5：R¹およびR³がヒドロキシの化合物（I－1－5）



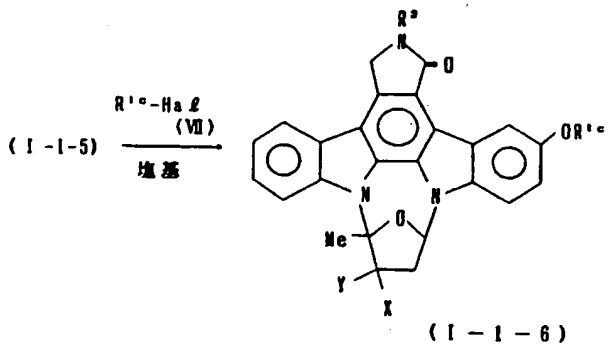

(I－1－5)

(式中、X，YおよびR³は前記と同義である)

アルカノイロキシ体（I－1－4）をアルカリ加水分解することにより、化合物（I－1－5）を得る。反応は化合物（I－1－4）とナトリウムメチラートまたはナトリウムエチラート等のナトリウム低級アルコキシドとを反応に不活性な溶媒中反応させる。塩基は化合物（I－1－4）に対し通常5～7当量用いる。不活性溶媒はジクロロメタン、THF等を包含する。反応は0℃～室温で行い、通常3～30分で終了する。

また、2置換アルカノイロキシ体（I－1－4′）から同様な条件で対応する2置換ヒドロキシ体（I－1－5′）を得る。

1－6：R¹および／またはR³がアルコキシの化合物（I－1－6）



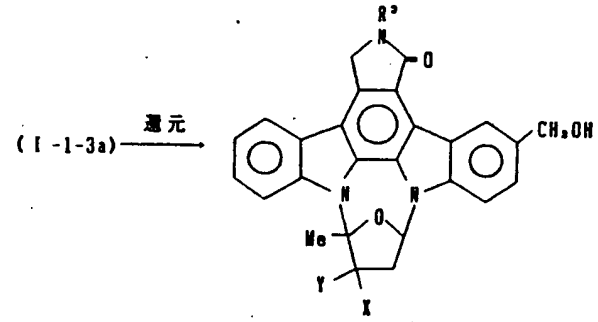

(I－1－6)

(式中、X，YおよびR³は前記と同義であり、R¹ᶜは低級アルキルを、Halはハロゲン原子を表わす)

ヒドロキシ体（I－1－5）と低級アルキルハライド（VII）とを反応に不活性な溶媒中塩基の存在下反応させて化合物（I－1－6）を得る。低級アルキルハライドは反応性に富むヨウ化物、臭化物が好ましい。塩基は水素化ナトリウム、カリウムt－ブトキシド等を包含する。化合物（VII）および塩基は化合物（I－1－5）に対し、通常1当量使用する。不活性溶媒はDMF、THF等を包含する。反応は通常0℃～常温で行い、20分～1時間で終了する。

また、2置換ヒドロキシ体（I－1－5′）から同様な条件で対応する2置換アルコキシ体（I－1－6′）を得る。

1－7：R¹および／またはR³がヒドロキシメチルの化合物（I－1－7）

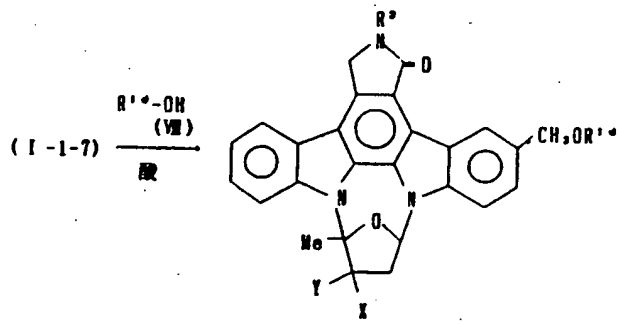



(I－1－7)

(式中、X，YおよびR³は前記と同義である)

アルデヒド体（I－1－3a）と適当な還元剤、例えば水素化ホウ素ナトリウムとを反応に不活性な溶媒中反応させて化合物（I－1－7）を得る。還元剤は化合物（I－1－3a）に対し通常2～3当量用いる。不活性溶媒としては通常クロロホルム－メタノール（1：1）の混合溶媒を用いる。反応は通常氷冷下で行い、0.5～1時間で終了する。

1－8：R¹および／またはR³がアルコキシメチルの化合物（I－1－8）



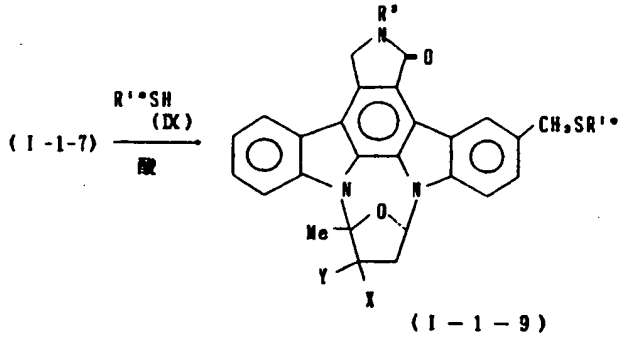

(I－1－8)

(式中、X，YおよびR³は前記と同義であり、R¹ᵈは低級アルキルである)

ヒドロキシメチル体（I－1－7）と低級アルキルアルコール（VIII）とを反応に不活性な溶媒中

適当な酸触媒、例えばカンファースルホン酸触媒の存在下反応させて化合物（Ⅰ－1－8）を得る。化合物（Ⅰ－1－7）に対し、通常化合物（Ⅷ）は大過剰、酸は1当量用いる。不活性溶媒はクロロホルム等を包含する。反応は通常加熱還流下に行い5～10時間で終了する。

1－9：R¹および／またはR³がアルキルチオメチルの化合物（Ⅰ－1－9）

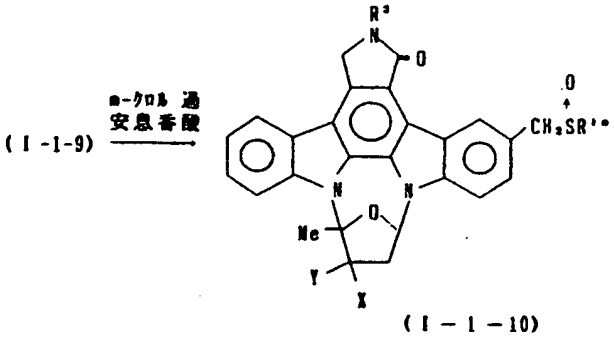



（Ⅰ－1－9）

（式中、X，YおよびR³は前記と同義であり、R¹⁰は低級アルキルである）

ヒドロキシメチル体（Ⅰ－1－7）と低級アルキルチオール（Ⅸ）とを反応に不活性な溶媒中適当な酸触媒、例えばカンファースルホン酸触媒の存在下反応させて化合物（Ⅰ－1－9）を得る。化合物（Ⅰ－1－7）に対し、通常化合物（Ⅸ）は5～10当量、酸は1当量用いる。不活性溶媒はクロロホルム等を包含する。反応は通常室温下に行い2～3時間で終了する。

1－10：R¹および／またはR³がアルキルスルフィニルメチルの化合物（Ⅰ－1－10）

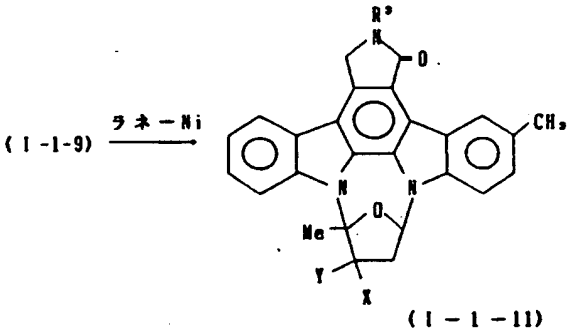



（Ⅰ－1－10）

（式中、X，Y，R³およびR¹⁰は前記と同義である）

アルキルチオメチル体（Ⅰ－1－9）をクロロホルム中1当量のm－クロル過安息香酸で室温撹拌下1～6時間酸化することにより化合物（Ⅰ－1－10）を得る。

1－11：R¹および／またはR³がメチルの化合物（Ⅰ－1－11）

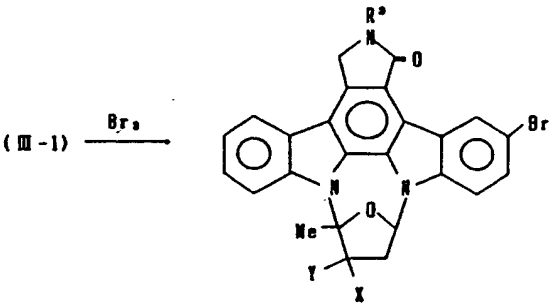



（Ⅰ－1－11）

（式中、X，YおよびR³は前記と同義である）

アルキルチオメチル体（Ⅰ－1－9）を酢酸エチル中化合物（Ⅰ－1－9）の重量に対し0.1～0.5倍重量のラネーニッケルで5～7時間加熱還流することにより化合物（Ⅰ－1－11）を得る。

1－12：R¹および／またはR³がブロムである合物（Ⅰ－1－12）

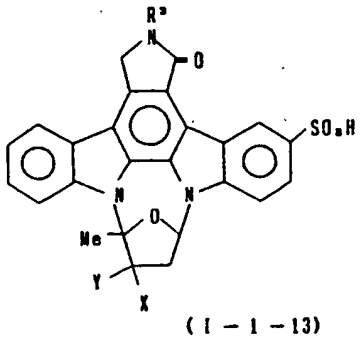



（Ⅰ－1－12）

（式中、X，YおよびR³は前記と同義である）

化合物（Ⅲ－1）と2～2.5当量の臭素とを通常ピリジン中室温撹拌下1日反応させることにより化合物（Ⅰ－1－12）を得る。

1－13：R¹および／またはR³がスルホン酸の化合物（Ⅰ－1－13）

(Ⅲ-1) $\xrightarrow{ClSO_3H}$ 

(Ⅰ-1-13)

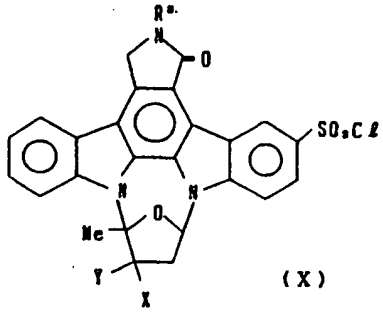
(式中、X，YおよびR³は前記と同義である)

化合物（Ⅲ－1）とクロロスルホン酸をモレキュラーシーブ4A存在下反応に不活性な溶媒、例えばクロロホルム中反応させることにより化合物（Ⅰ－1－13）を得ることができる。クロロスルホン酸は化合物（Ⅲ－1）に対し2～2.5当量、モレキュラーシーブ4Aは化合物（Ⅲ－1）と同重量用いられる。反応は－10～10℃で行われ、1～6時間で終了する。

1－14：R¹および／またはR²がスルホン酸アミドの化合物（Ⅰ－1－14）

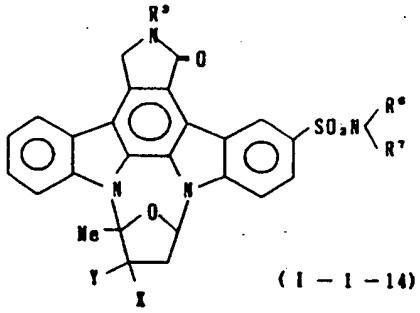
スルホン酸体（Ⅰ－1－13）と五塩化リンおよびオキシ塩化リンとを1～6時間加熱還流下反応させてスルホニククロライド体（X）を得る。化合物（Ⅰ－1－13）に対し、五塩化リンは2当量、オキシ塩化リンは10当量用いられる。次いで化合物（X）とアミン（XⅠ）を塩基存在下、反応に不活性な溶媒、例えばDMF中反応させることにより化合物（Ⅰ－1－14）を得ることができる。塩基としてはピリジン、トリエチルアミン等が含まれ、化合物（X）に対し2～3当量用いられる。化合物（XⅠ）は化合物（X）に対し4～5当量用いられる。反応は0℃～室温で1～12時間で終了する。

1－15：R¹および／またはR²が-OCOOR⁶である化合物（Ⅰ－1－15）

(Ⅰ-1-13) $\xrightarrow{PCl_5/POCl_3}$ 

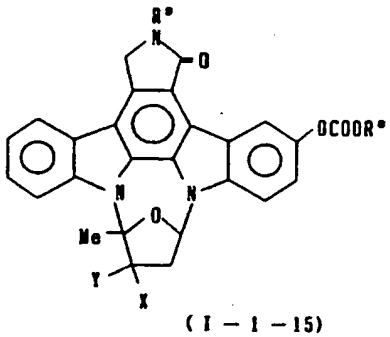
(X)

$\xrightarrow{HN\begin{matrix}R^4\\R^5\end{matrix}}$ (XⅠ)



(Ⅰ－1－14)

(式中、X，Y，R³，R⁴およびR⁵は前記と同義である)

(Ⅰ-1-5) $\xrightarrow[\text{塩基}]{R^6OCOCl\ (XⅡ)}$ 

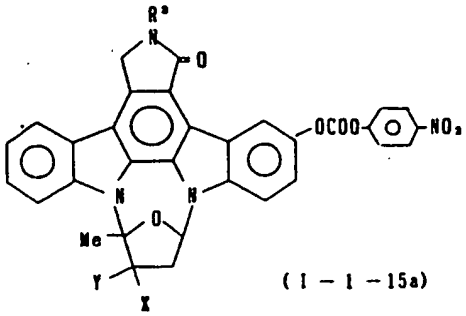
(Ⅰ－1－15)

(式中、X，Y，R³およびR⁶は前記と同義である)

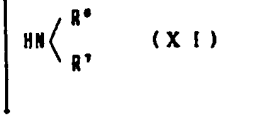
ヒドロキシ体（Ⅰ－1－5）と酸クロリド（XⅡ）とを適当な塩基例えばトリエチルアミン存在下反応に不活性な溶媒、例えばTHF中反応させることにより化合物（Ⅰ－1－15）を得る。

化合物（Ⅰ－1－5）に対し化合物（XⅡ）は1～2当量、塩基は2～2.5当量用いられる。反応は通常0℃～室温で行われ、0.5～6時間で終了する。

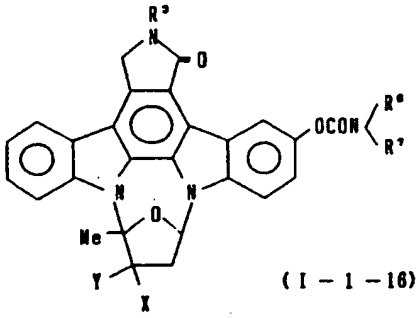
1－16：R¹および／またはR²が-OCON$\begin{matrix}R^4\\R^5\end{matrix}$の化合物（Ⅰ－1－16）



(I－1－15a)



(XI)

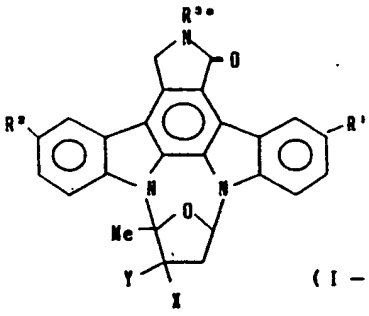


(I－1－16)



$R^{3a}$-Hal (XIII)

塩基



(I－2－1)

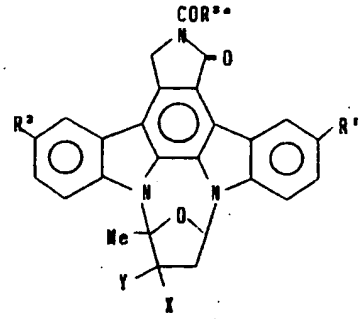
(式中、X，Y，R'，$R^3$およびHalは前記と同義であり、$R^{3a}$は低級アルキルである)

反応は化合物(III－2)〔化合物(I)において$R^3$が水素である化合物および化合物(II)〕と低級アルキルハライド(XIII)とを反応に不活性な溶媒中塩基の存在下反応させて化合物(I－2－1)を得る。化合物(XIII)は反応性に富むヨウ化物、臭化物が好ましい。塩基は水素化ナトリウム、カリウムt－ブトキシド等を包含する。化合物(XIII)および塩基は化合物(III－2)に対し、通常1～3当量使用する。不活性溶媒はDMF、THF等を包含する。反応は通常0℃～常温で行い、20分～1時間で終了する。

(式中、X，Y，R'，$R^3$および$R^{3a}$は前記と同義である)

$R^{3a}$-CO)$_2$O または $R^{3a}$COCl

(III-2) ——塩基——



(I－2－2)

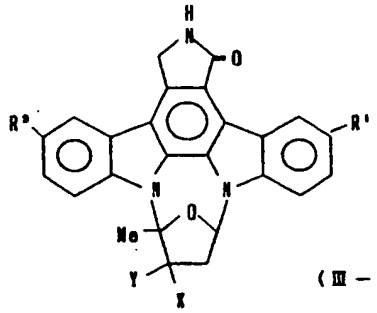
反応は、(III－2)とアシル化剤〔($R^{3a}$CO)$_2$Oまたは$R^{3a}$COCl等〕とより方法1－2cと同様の条件で行うことにより化合物(I－2－2)を

(式中、X，Y，R'，$R^3$および$R^{3a}$は前記と同義である)

p－ニトロフェノキシ体(I－1－15a)〔化合物(I－1－15)で$R^3$がp－ニトロフェニルである化合物〕とアミン(XI)とを反応に不活性な溶媒、例えばDMF中反応させることにより化合物(I－1－16)を得ることができる。化合物(XI)は化合物(I－1－15a)に対し1～1.2当量用いられる。反応は通常0℃～室温で行われ0.5～6時間で終了する。

方法2：$R^3$に官能基を有する化合物(I－2)の合成

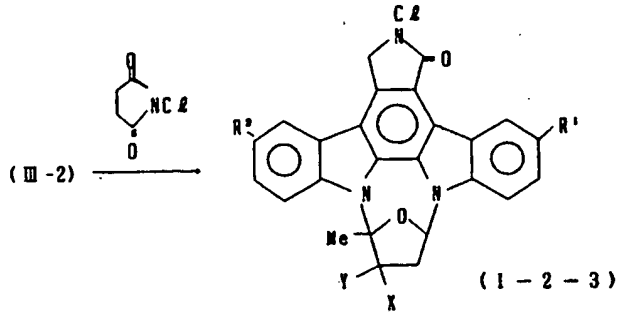
2－1：$R^3$がアルキルの化合物(I－2－1)



(III－2)

得る。

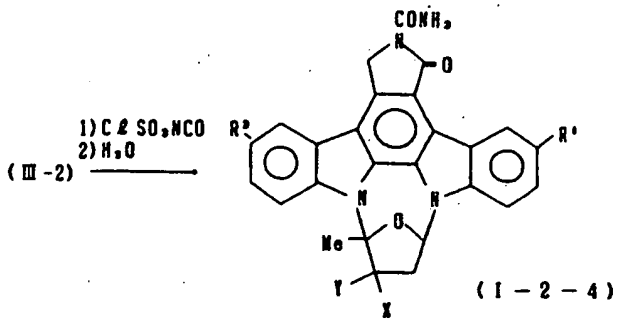
2－3：R³が塩素の化合物（I－2－3）



（式中、X，Y，R¹およびR³は前記と同義である）

化合物（III－2）と適当なクロル化剤、例えばN－クロロコハク酸イミド（NCS）とを反応に不活性な溶媒中反応させて化合物（I－2－3）を製造する。クロル化剤は化合物（III－2）に対し通常1当量用いる。不活性溶媒はクロロホルム、ジクロロメタン等を包含する。反応は加熱還流下に行い、通常1～24時間で終了する。

2－4：R³がカルバモイルの化合物（I-2-4）

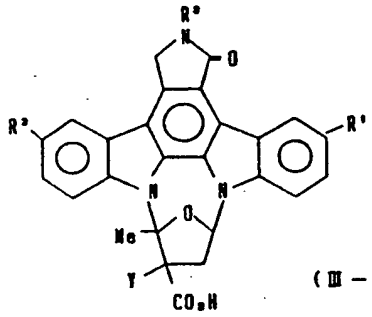


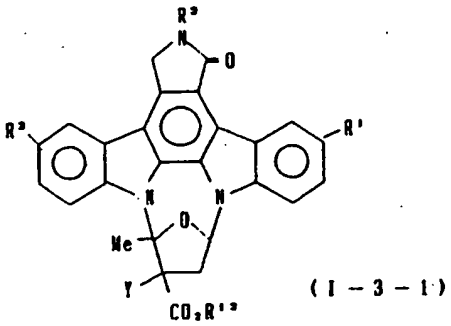
（式中、X，Y，R¹およびR³は前記と同義である）

化合物（III－2）と適当なカルバモイル化試薬、例えばクロロスルホニルイソシアネートを不活性な溶媒、例えばTHF中、氷冷下1～3時間撹拌し、ついで水を加え0.5～1時間、70～80℃で加熱撹拌することにより化合物（I－2－4）を得ることができる。カルバモイル化試薬は化合物（III－2）に対し1～10当量、水は大過剰用いる。

方法3：Xを修飾した化合物（I－3）の合成

3－1：Xがアルコキシカルボニルの化合物（I－3－1）

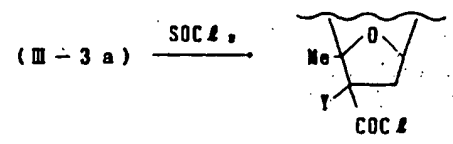


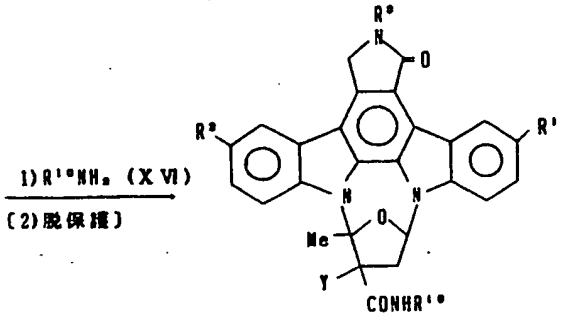


（式中、Y，R¹，R³およびR⁹は前記と同義でありR¹⁰は低級アルキルである）

反応はカルボン酸（III－3a）〔化合物（I）において、Xがカルボキシルである化合物〕にアルコール（XIV）および過剰の塩化チオニルを加え、加熱還流することにより化合物（I－3－1）を得ることができる。塩化チオニルは、溶媒をかねて用いる化合物（XIV）の10分の1程度（体積比）の量が通常用いられる。反応は80～100℃の範囲内で行われ、1時間～1日でほぼ終了する。

3－2：Xが-CONHR¹⁰の化合物（I－3－2）






(I－3－2)

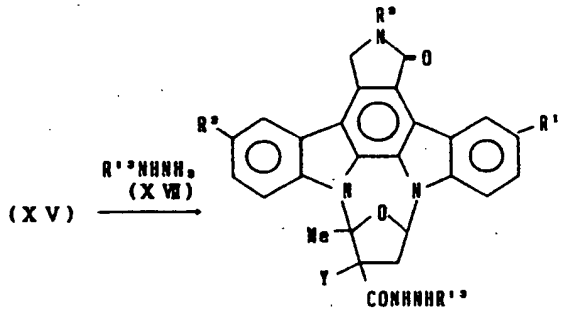
(式中、Y，R¹，R²，R⁰およびR'⁰は前記と同義である)

化合物(Ⅲ－3a)を塩化チオニル中加熱還流して酸クロリド(XV)を得る。

化合物(XV)とα－アミノ酸低級アルキルエステルもしくはベンジルエステル(XVI)とを不活性溶媒中反応させて化合物(I－3－2)を得る。化合物(XVI)は化合物(XV)に対し通常10当量程度用いる。化合物(XVI)の酸塩、例えば塩酸塩を用いる場合は当モルの3級アミン、例えばトリエチルアミンを加える必要がある。不活性溶媒はクロロホルム等を包含する。反応は通常0℃～室温攪拌下に行い、1時間～1日で終了する。

また、化合物(I－3－2)で、該アミノ酸のカルボキシル基が遊離の化合物(I－3－2a)を所望の場合はエステル体(I－3－2b)より常法通り脱保護することにより得られる。例えば化合物(I－3－2b)が低級アルキルエステルの場合、化合物(I－3－2b)を含水THF中4～5当量の水酸化ナトリウムまたは水酸化カリウムで室温下0.5～6時間加水分解することにより化合物(I－3－2a)を得る。また、ベンジルエステルの場合、方法1－2aに記載した接触還元法により同じく化合物(I－3－2a)を得る。

3－3：Xがアルキルヒドラジノカルボニルの化合物(I－3－3)

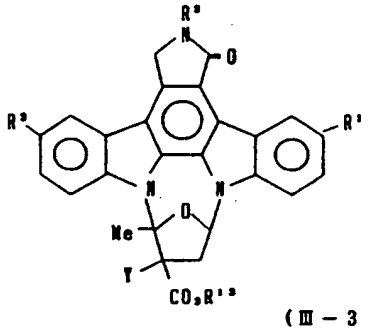



(I－3－3)

(式中、Y，R¹，R²，R⁰およびR'⁰は前記と同義である)

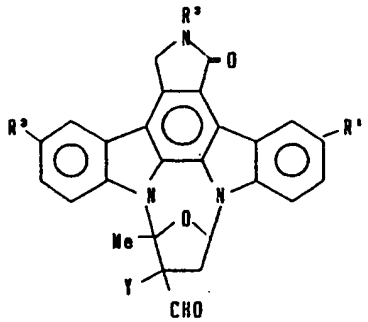
反応は方法3－2で得られる酸クロリド(XV)とヒドラジン類(XVII)とより方法3－2と同様の条件で行うことにより化合物(I－3－3)を得る。

3－4：Xがホルミルの化合物(I－3－4)




(Ⅲ－3b)

還元

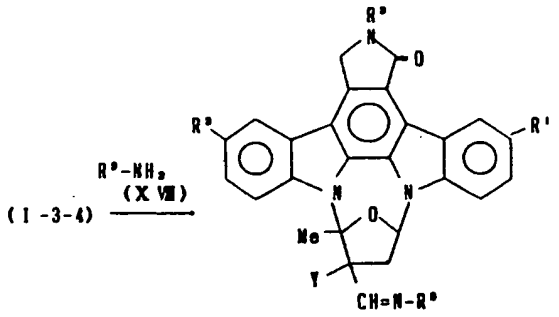



(I－3－4)

（式中、Y，R¹，R²，R³およびR''は前記と同義である）

反応はエステル体（Ⅲ－３ｂ）〔化合物（Ⅰ－３－１）およびK－２５２〕と適当な還元試薬、例えば水素化リチウムアルミニウムとを通常THF中反応させて化合物（Ⅰ－３－４）を得る。還元試薬は通常１当量使用する。反応は水冷下に行い通常１時間で終了する。

３－５：Xが -CH=N-R³ の化合物（Ⅰ－３－５）

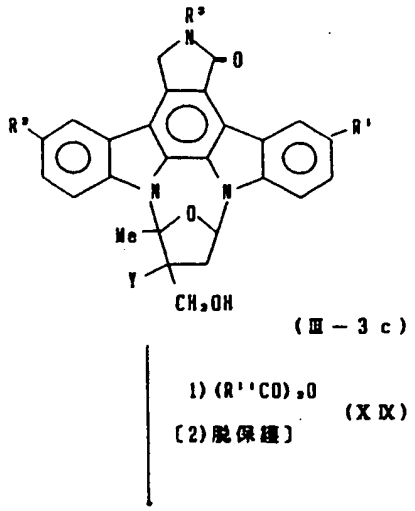


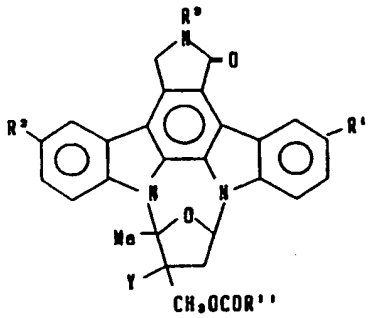

（Ⅰ－３－５）

（式中、Y，R¹，R²，R³およびR³は前記と同義である）

アルデヒド体（Ⅰ－３－４）とアミン類（XⅧ）とを通常ＴＨＦ－水（１０：１）の混合溶媒中反応させて化合物（Ⅰ－３－５）を得る。化合物（XⅧ）は通常塩酸塩、臭化水素酸塩または硫酸塩の形で５～１０当量用いる。反応は通常室温下で行い１時間～１日で終了する。

３－６：Xが -CH₂OCOR'' の化合物（Ⅰ－３－６）



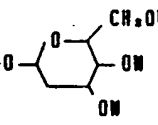

（Ⅰ－３－６）

（式中、Y，R¹，R²，R³およびR''は前記と同義である）

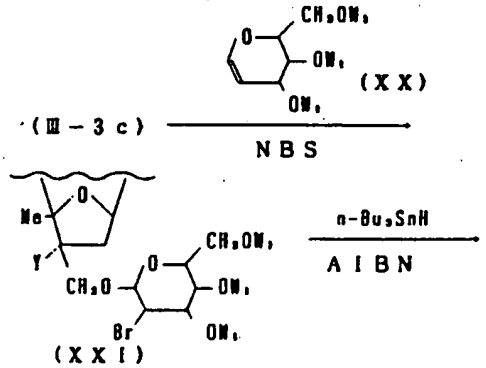
反応はヒドロキシメチル体（Ⅲ－３ｃ）〔化合物（Ⅰ）において、Xがヒドロキシメチルである化合物および化合物（Ⅱｂ）〕とα－アミノ酸の酸無水物（XⅨ）と適当な溶媒中、塩基存在下で反応させることにより化合物（Ⅰ－３－６）を得る。塩基としてはトリエチルアミン、N，N－ジメチルアミノピリジン等が化合物（Ⅲ－３ｃ）に対し１～2.４当量用いられる。化合物（XⅨ）は化合物（Ⅲ－３ｃ）に対し１～1.２当量用いられる。反応溶媒としてＴＨＦ、ＤＭＦ等が用いられ、反応は通常室温～１００℃で行われ１～１２時間で終了する。

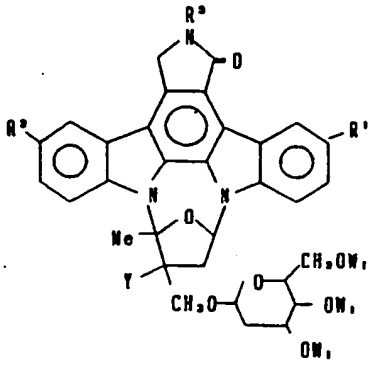
また、化合物（Ⅰ－３－６）で該アミノ酸のアミノ基が遊離の化合物（Ⅰ－３－６ａ）を所望の場合は、常法により脱保護すればよい。例えば保護基がベンジルオキシカルボニルの場合、方法１－２ａに記載した接触還元法により化合物（Ⅰ－３－６ａ）を得る。

３－７：Xが -CH₂Zの化合物（Ⅰ－３－７）

３－７ａ：Zが  の化合物

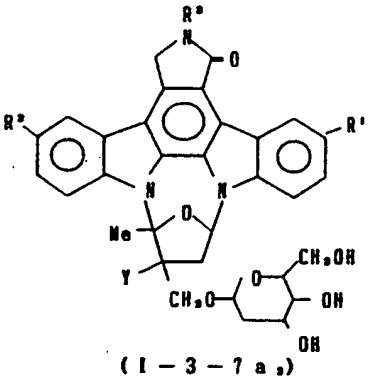
（Ⅰ－３－７ａ）





(I－3－7a₁)

〔脱保護〕



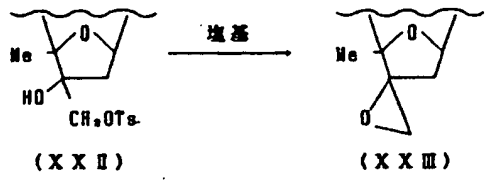
(I－3－7a₂)

(式中、W₁はWの定義中水素以外の基を表わし、Y，R¹，R²，R³およびWは前記と同義である。)

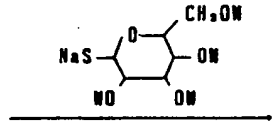
反応はまず、ヒドロキシメチル体(III－3c)とトリ－O－置換－グルカール類(XX)を反応に不活性な溶媒、例えばクロロホルム中N－ブロモコハク酸イミド(NBS)存在下反応させることによりグリコシド体(XXI)を得る。化合物(III－3c)に対しNBSは1～5当量、化合物(XX)は1～1.5当量用いられる。反応は通常室温遮光下6時間～1日で終了する。

次いで、化合物(XXI)と水素化トリブチル錫をα，α'－アゾビスイソブチロニトリル(AIBN)存在下、反応に不活性な溶媒、例えばトルエン中反応させることにより脱ブロム体(I－3－7a₁)を得る。水素化トリブチル錫およびAIBNは化合物(XXI)に対し1.5～2当量用いられる。反応は通常60～100℃で1～12時間で終了する。

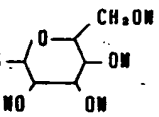
また化合物(I－3－7a)中、Wが水素の化合物(I－3－7a₂)を所望の場合、化合物(I－3－7a₁)の保護基を常法により脱保護すればよい。例えば化合物(I－3－7a₁)でW₁がアセチルの場合、該化合物(I－3－7a₁)を含水THF中3～6当量の水酸化ナトリウムまたはアンモニア水で室温下1～12時間反応させることにより化合物(I－3－7a₂)を得ることができる。またW₁がベンジルの場合、方法1－2aに記載の接触還元法が適用される。



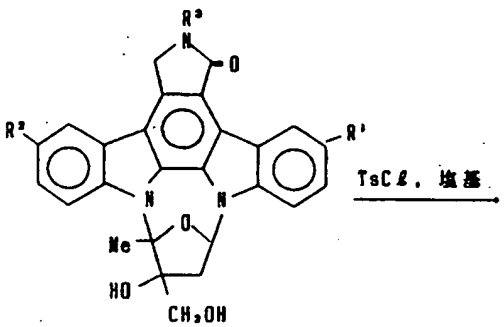
(XXII)　(XXIII)



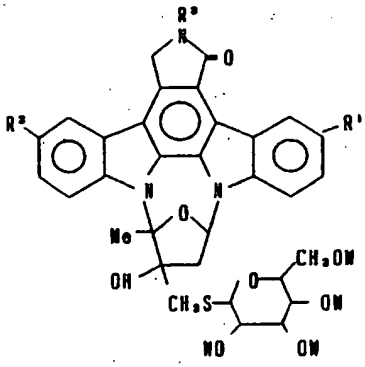
(XXIV)

3－7b：Zが -S-  の化合物

(I－3－7b)



(III－3c)



(I－3－7b)

(式中、R¹，R²，R³およびWは前記と同義

である）

反応はまず、ヒドロキシメチル体（Ⅲ－３ｃ）′〔化合物（Ⅲ－３ｃ）中Ｙがヒドロキシである化合物〕とｐ－トルエンスルホニルクロリド（TsCℓ）とを不活性溶媒中塩基の存在下反応させてトシル体（ＸＸⅡ）を得る。塩基はトリエチルアミン、ピリジン、Ｎ，Ｎ－ジメチルアミノピリジン、水素化ナトリウム等を、不活性溶媒はＴＨＦ、ジオキサン、クロロホルム等を包含する。ｐ－トルエンスルホニルクロリドおよび塩基を通常化合物（Ⅲ－３ｃ）′にたいし２～３当量用いる。反応は通常０℃～室温で行い、１時間～１日で終了する。

次いで化合物（ＸＸⅡ）に水素化ナトリウム１～２当量を作用させることにより、エポキシド（ＸＸⅢ）を得る。反応は、通常ＴＨＦまたはジオキサン中、室温で行われ、１～６時間で終了する。

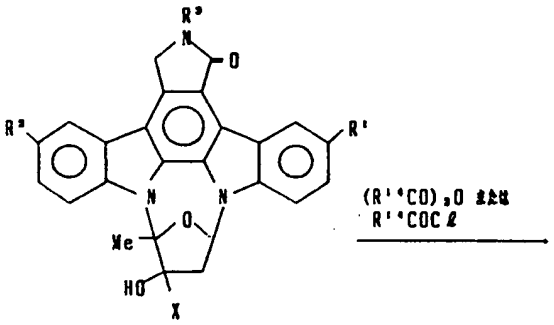
さらに化合物（ＸＸⅢ）とチオグルコースナトリウム塩類（ＸＸⅣ）とを反応に不活性な溶媒

（式中、Ｙ，Ｒ¹，Ｒ²およびＲ³は前記と同義である）

反応は化合物（Ⅰ－３－１）と適当な還元剤、例えば水素化ホウ素ナトリウムを適当な不活性溶媒、例えば含水ＴＨＦ中で反応させることにより化合物（Ⅰ－３－８）を得ることができる。還元剤は３～５当量用いられる。反応は、通常氷冷下行われ、１～６時間で終了する。

方法４：Ｙを修飾した化合物（Ⅰ－４）の合成

４－１：Ｙがアルカノイロキシの化合物（Ⅰ－４－１）



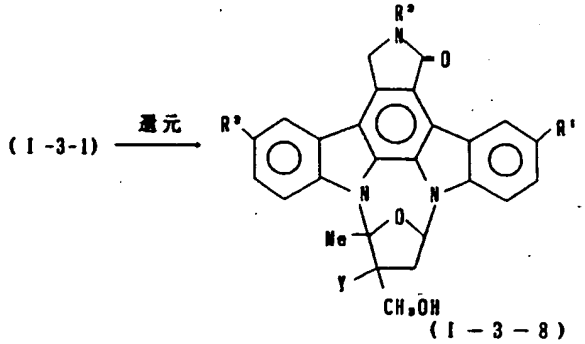

（Ⅲ－４ａ）

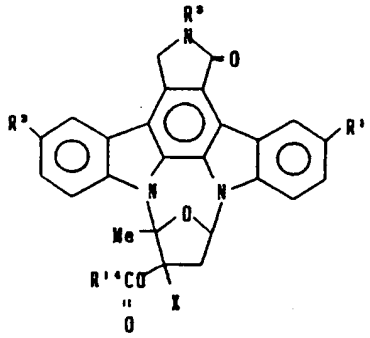
例えばＤＭＦ中反応させることにより化合物（Ⅰ－３－７ｂ）を得る。

化合物（ＸＸⅣ）は化合物（ＸＸⅢ）に対して１～1.５当量用いられる。反応は通常室温～５０℃で行われ、１～１２時間で終了する。

３－８：Ｚがヒドロキシメチルの化合物（Ⅰ－３－８）

Ｚがヒドロキシメチルの化合物（Ⅰ－３－８）は、化合物（Ⅱｂ）を出発原料とすることも可能であるが、Ｚがアルコキシカルボニルの化合物（Ⅰ－３－１）を還元することによっても得ることができる。



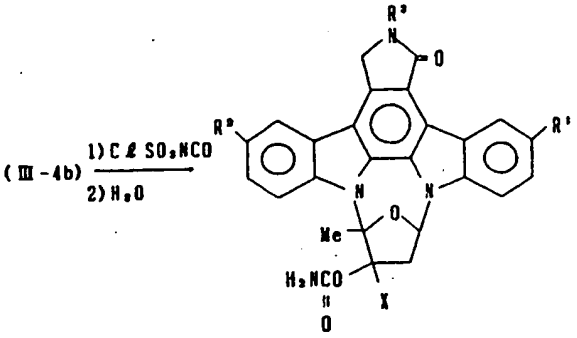

（Ⅰ－４－１）

（式中、Ｘ，Ｒ¹，Ｒ²およびＲ³は前記と同義であり、Ｒ''は低級アルキルである）

反応はヒドロキシ体（Ⅲ－４ａ）〔化合物（Ⅰ）においてＹがヒドロキシである化合物〕とアシル化剤〔(R''CO)₂O またはR''COCℓ等〕とを塩基存在下反応させることによりアシル体（Ⅰ－４－１）を得る。塩基はピリジン、トリエチルアミン等を包含する。アシル化剤は化合物（Ⅲ－４ａ）に対し１～２当量用いる。反応は通常ピリジンを溶媒とし室温下で行い１～１２時間で終了する。

４－２：Ｙがカルバモイルオキシの化合物（Ⅰ－

4－2）



（Ⅲ-4b）

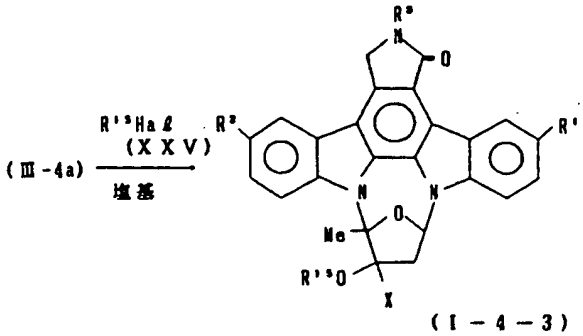
1) $ClSO_2NCO$
2) $H_2O$

（Ⅰ－4－2）

（式中、X，$R^1$，$R^2$および$R^3$は前記と同義である）

反応は化合物（Ⅲ－4b）〔化合物（Ⅲ－4a）および化合物（Ⅱ）〕とカルバモイル化試薬、例えばクロロスルホニルイソシアネートとから方法2－4と同様の条件で行うことにより化合物（Ⅰ－4－2）を得る。

4－3：Yがアルコキシの化合物（Ⅰ－4－3）



（Ⅲ-4a）

$R^{13}Hal$
（ⅩⅤ）
塩基

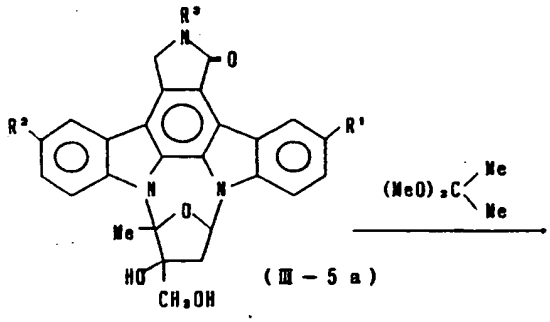
（Ⅰ－4－3）

（式中、X，$R^1$，$R^2$，$R^3$および$R^{13}Hal$は前記と同義であり$R^{13}$は低級アルキルである）

化合物（Ⅲ－4a）と低級アルキルハライド（ⅩⅤ）とを反応に不活性な溶媒中水素化ナトリウムまたはカリウムt－ブトキシドのような塩基の存在下反応させてアルキル体（Ⅰ－4－3）を得る。化合物（ⅩⅤ）は反応性に富むヨウ化物または臭化物が好ましい。化合物（ⅩⅤ）および塩基は化合物(Ⅲ－4a)に対し1当量用いる。不活性溶媒はDMF、THF等を包含する。反応は通常0℃～室温で行い、20分～1時間で終了する。

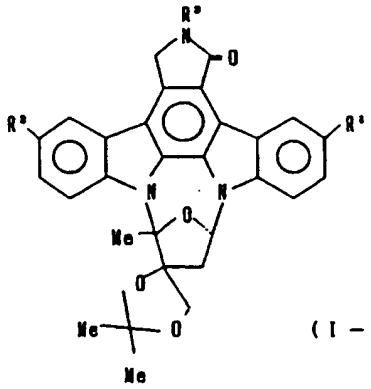
方法5：－Y－X－の化合物（Ⅰ－5）の合成

5－1：－Y－X－が $-O-C(CH_3)_2-O-CH_2-$ の化合物（Ⅰ－5－1）



（Ⅲ－5a）

$(MeO)_2C(Me)_2$



（Ⅰ－5－1）

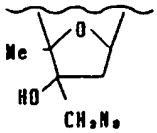
（式中、$R^1$，$R^2$および$R^3$は前記と同義である）

反応は化合物（Ⅲ－5a）〔化合物（Ⅰ）において、Xがヒドロキシメチルおよびヒドロキシである化合物および化合物（Ⅱb）〕と通常5当量の2,2－ジメトキシプロパンをクロロホルム中適当な酸触媒、例えばカンファースルホン酸〔化合物（Ⅲ－5a）の0.1～0.5当量〕の存在下加熱還流下1～12時間反応させて化合物（Ⅰ－5－1）を得る。

5－2：-Y-X- が $-OC(=S)NHCH_2-$ の化合物（Ⅰ－5－2）

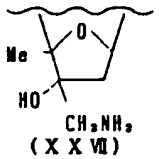
（ⅩⅩⅡ）

$NaN_3$



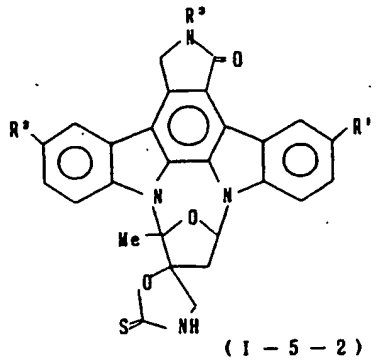
（ⅩⅩⅥ）

$LiAlH_4$



（ⅩⅩⅦ）

1,1'－チオカルボニルジイミダゾール



(I－5－2)

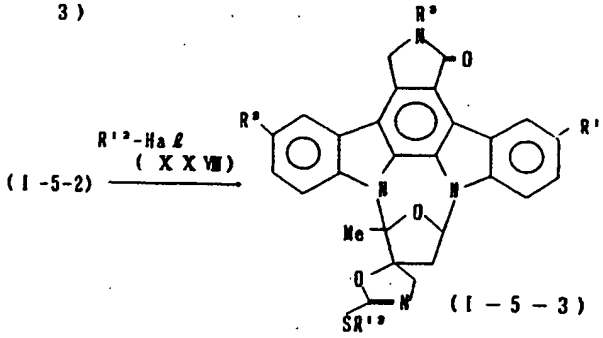
(式中、R¹, R²およびR³は前記と同義である)

反応はまず、方法3－7bで得られるトシル体(XXII)と通常1～2当量のアジ化ナトリウムとを不活性溶媒中反応させてアジド体(XXVI)を得る。不活性溶媒はDMF、ジメチルスルホキシド、THF等を用いる。反応は通常室温で行い、1時間～1日で終了する。

次いで化合物(XXVI)と2～6当量の水素化リチウムアルミニウムとを不活性溶媒中反応させてアミノ体(XXVII)を得る。不活性溶媒はTHF、ジオキサン等を包含する。反応は通常0℃～室温で行い1～6時間以内で終了する。

さらに化合物(XXVII)と1～2当量の1,1'－チオカルボニルジイミダゾールとを通常DMF中氷冷下1～2時間反応させて化合物(I－5－2)を得る。

5－3：-Y-X-が $-O-\overset{SR^{12}}{\overset{|}{C}}=N-CH_2-$ の化合物(I－53)



(I－5－3)

(式中、R¹, R², R³, R¹²およびHalは前記と同義である)

方法5－2で得られる化合物(I－5－2)と低級アルキルハライド(XXVIII)とを通常DMF中反応させて化合物(I－5－3)を得る。化合物(XXVIII)は反応性に富むヨウ化物が好ましい。

反応は通常室温下で行い1～12時間で終了する。

以上、方法1～5を適宜組合わせて実施することにより、所望の位置に所望の官能基を有する化合物(I)を得ることができる。

上記各工程終了後の生成物の単離、精製は通常の有機合成で用いられる方法、例えば抽出、結晶化、クロマトグラフィー等を適宜組み合わせて行うことができる。

化合物(I)およびその薬理的に許容される塩はC－キナーゼ阻害活性、抗ヒスタミン遊離抑制活性、血小板凝集抑制活性、抗炎症活性等を有し、抗アレルギー剤、抗血栓剤、抗炎症剤等の活性成分として有用であると期待される。かかる医薬製剤は通常有効量の化合物(I)もしくはその薬理的に許容される塩および少なくとも1種薬理的に許容される医薬担体を含有してなる。医薬製剤の投与量は投与方法、治療期間、年令、体重等によって異なるが、経口または非経口(例えば注射、塗布、吸入等)で人に対し1日あたり0.5～100mg／kgが適当である。製剤形態は錠剤、丸剤、粉末剤、顆粒剤、カプセル剤、坐剤、注射等を包含する。製剤化に際しては常用の医薬担体例えば乳糖、デキストロース、蔗糖、ソルビトール、マニトール、グルコース、シクロデキストリン、タルク、殿粉、メチルセルロース、ゼラチン、アラビアゴム、ポリエチレングリコール、カルボキシメチルセルロース、ヒドロキシプロピルセルロース、安息香酸ナトリウム、亜硫酸水素ナトリウム、ステアリン酸アルミニウム、ステアリン酸マグネシウム、植物油、白色ワセリン、注射用蒸留水等が適宜選択して常法に用いられる。本製剤は組成物中化合物(I)またはその薬理的に許容される塩を0.01～85重量%含む。

さらに、化合物(I)は、ヒト子宮頸癌細胞ヘラ(Hela)細胞、ヒト乳癌細胞MCF7、ヒト結腸腺細胞COLO320DM、ヒト肺分化型扁平上皮癌細胞PC－10等に対して顕著な細胞生育阻害活性を示し、従って化合物(I)を有効成分とする抗腫瘍剤が提供される。

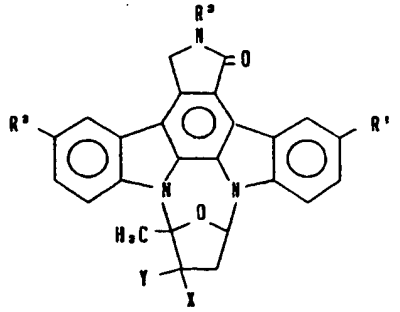
化合物(I)を抗腫瘍剤として用いる場合には、

各々の化合物を、0.01～20mg／kgの投与量で、生理食塩水、ブドウ糖、ラクトース、マンニット注射液に溶解して注射剤として通常静脈内に投与する。また日本薬局方に基づいて凍結乾燥してもよいし、塩化ナトリウムを加えた粉末注射剤としてもよい。さらに医薬品的用途を満たした塩類のような、よく知られた薬学的に許容されている希釈剤、補助剤および／または担体を含んでいてもよい。注射剤として使用する場合には溶解度を高めるための助剤を併用するのが好ましい場合がある。投与量は年齢や症状により適宜増減できる。投与スケジュールも症状や投与量によって変えることができるが、たとえば1日1回（単回投与または連日投与）、週1～3回あるいは3週間に1回などの間歇投与がある。また同様の投与量、投与方法で経口投与、直腸投与も可能である。経口投与に際しては適当な補助剤と共に、錠剤、粉剤、粒剤、シロップ剤、坐剤等として投与できる。

**実施例**

次に上記製法によって得られる化合物（I）の代表例を第1表に、その中間体を第2表に示す。またこれらの化合物（I）の製造例を実施例に、その中間体の製造例を参考例に、代表的化合物（I）の薬理活性を実験例に、代表的化合物（I）の製剤例を参考例に示す。

第　1　表



（I）

化合物　実施例

| No. | No. | R¹ | R² | R³ | X | Y | 塩 |
|---|---|---|---|---|---|---|---|
| 1 | 1 | $NH_2$ | H | Ac | $CO_2Me$ | OAc | |
| 2 | 1 | $NH_2$ | $NH_2$ | Ac | $CO_2Me$ | OAc | |
| 3 | 2 | $NH_2$ | H | H | $CO_2Me$ | OH | HCℓ |
| 4 | 3 | $NH_2$ | $NH_2$ | H | $CO_2Me$ | OH | |
| 5 | 4 | $NMe_2$ | H | H | $CO_2Me$ | OH | HCℓ |

化合物　実施例

| No. | No. | R¹ | R² | R³ | X | Y | 塩 |
|---|---|---|---|---|---|---|---|
| 6 | 5 | $NBt_2$ | H | H | $CO_2Me$ | OH | HCℓ |
| 7 | 6 | NHAc | H | Ac | $CO_2Me$ | OAc | |
| 8 | 7 | NHAc | H | H | $CO_2Me$ | OH | |
| 9 | 8 | NHCOn-Pr | H | Ac | $CO_2Me$ | OAc | |
| 10 | 9 | NHCOn-Pr | H | H | $CO_2Me$ | OH | |
| 11 | 10 | NHCOn-Bu | H | Ac | $CO_2Me$ | OAc | |
| 12 | 11 | NHCOn-Bu | H | H | $CO_2Me$ | OH | |
| 13 | 12 | NHCONHMe | H | H | $CO_2Me$ | OH | |
| 14 | 13 | NHCONHBt | H | H | $CO_2Me$ | OH | |
| 15 | 14 | NHCONHPh | H | H | $CO_2Me$ | OH | |
| 16 | 15 | $NHCONH_2$ | H | H | $CO_2Me$ | OH | |
| 17 | 16 | COMe | H | Ac | $CO_2Me$ | OAc | |
| 18 | 16 | COMe | COMe | Ac | $CO_2Me$ | OAc | |
| 19 | 17 | CHO | H | Ac | $CO_2Me$ | OAc | |
| 20 | 17 | CHO | CHO | Ac | $CO_2Me$ | OAc | |
| 21 | 18 | COMe | H | H | $CO_2Me$ | OH | |
| 22 | 19 | CHO | H | H | $CO_2Me$ | OH | |
| 23 | 20 | CHO | CHO | H | $CO_2Me$ | OH | |

化合物　実施例

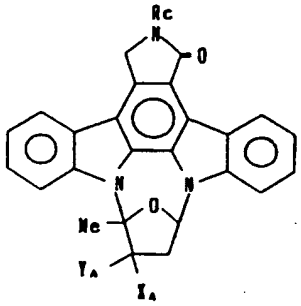
| No. | No. | R¹ | R² | R³ | X | Y | 塩 |
|---|---|---|---|---|---|---|---|
| 24 | 21 | OH | H | H | $CO_2Me$ | OH | |
| 25 | 22 | OH | OH | H | $CO_2Me$ | OH | |
| 26 | 23 | OMe | H | H | $CO_2Me$ | OH | |
| 27 | 24 | OBt | H | H | $CO_2Me$ | OH | |
| 28 | 25 | On-Pr | H | H | $CO_2Me$ | OH | |
| 29 | 26 | Oi-Pr | H | H | $CO_2Me$ | OH | |
| 30 | 27 | On-Bu | H | H | $CO_2Me$ | OH | |
| 31 | 28 | $CH_2OH$ | H | Ac | $CO_2Me$ | OAc | |
| 32 | 29 | $CH_2SBt$ | H | Ac | $CO_2Me$ | OAc | |
| 33 | 30 | Me | H | Ac | $CO_2Me$ | OAc | |
| 34 | 31 | $CH_2SBt$ | H | H | $CO_2Me$ | OH | |
| 35 | 32 | Me | H | H | $CO_2Me$ | OH | |
| 36 | 33 | $CH_2S(O)Bt$ | H | H | $CO_2Me$ | OH | |
| 37 | 34 | Br | H | H | $CO_2Me$ | OH | |
| 38 | 35 | H | H | H | CONHNHMe | OAc | |
| 39 | 36 | H | H | H | $CONHCH_2CO_2Me$ | OAc | |

| 化合物 No. | 実施例 No. | R¹ | R² | R³ | X | Y | 塩 |
|---|---|---|---|---|---|---|---|
| 40 | 37 | H | H | H |  | OAc | |
| 41 | 38 | H | H | H |  | OAc | NH₂ |
| 42 | 39 | H | H | H | CONHCH₂CO₂H | OH | NH₂ |
| 43 | 40 | H | H | H | CHO | OH | |
| 44 | 41 | H | H | H | CH=NOH | OH | |
| 45 | 42 | H | H | H | CH=NNHCONH₂ | OH | |
| 46 | 43 | H | H | H |  | OH | |
| 47 | 44 | H | H | H |  | OH | |
| 48 | 45 | H | H | Me | CO₂Me | OMe | |
| 49 | 46 | H | H | Cℓ | CO₂Me | OH | |
| 50 | 47 | H | H | H | -CH₂NHC(=S)-O- | | |
| 51 | 48 | H | H | H | -CH₂N=C(SMe)-O- | | |
| 52 | 49 | H | H | H | -CH₂-O-C(CH₃)₂-O- | | |

| 化合物 No. | 実施例 No. | R¹ | R² | R³ | X | Y | 塩 |
|---|---|---|---|---|---|---|---|
| 53 | 50 | NO₂ | H | H | CO₂Me | OH | |
| 54 | 51 | H | H | CONH₂ | CO₂Me | OCONH₂ | |
| 55 | 52 | H | H | H | CH₂OCOCH₂NHCbz | OH | |
| 56 | 53 | H | H | H | CH₂OCOCH₂NH₂ | OH | HCℓ |
| 57 | 54 | H | H | H |  | OH | |
| 58 | 55 | H | H | H |  | OH | |
| 59 | 56 | H | H | H |  | OH | |
| 60 | 57 | SO₃H | H | H | CO₂Me | OH | |
| 61 | 58 |  | H | H | CO₂Me | OH | |
| 62 | 59 |  | H | H | CO₂Me | OH | |
| 63 | 60 | * | H | H | CO₂Me | OH | |
| 64 | 61 | CH₂OBt | H | Ac | CO₂Me | OAc | |
| 65 | 62 | CH₂OBt | H | H | CO₂Me | OH | |
| 66 | 63 | CH₂OBt | H | H | CH₂OH | OH | |

* 

第 2 表 中 間 体



| 化合物No. | 参考例No. | $X_A$ | $Y_A$ | $R_c$ |
|---|---|---|---|---|
| a | 1 | $CO_2Bt$ | OH | H |
| b | 2 | $CO_2Me$ | OMe | H |
| c | 3 | $CO_2H$ | OAc | H |
| d | 4 | COCℓ | OAc | H |
| e | 5 | $CH_2OH$ | OH | H |
| f | 6 | $CH_2OTs$ | OH | H |
| g | 7 | $CH_2N_3$ | OH | H |
| h | 8 | $CH_2NH_2$ | OH | H |
| i | 9 | $CO_2Me$ | OAc | Ac |
| j | 10 | — $CH_2O$ — | | H |

実施例 1

参考例 9 で得られる化合物 i （Ⅲ-1；X=$CO_2Me$, Y=OAc, $R^3$=Ac) 5.51 g(10 mmol) をスルホラン 100 mℓおよびクロロホルム 50 mℓに溶解し、ニトロニウムテトラフルオロボレート 2.8 g (10.5 mmol) を加え、80℃にて 2 時間加熱した。クロロホルムを減圧下留去後、水 200 mℓを加え析出物を吸引ろ取し、水、メタノールで洗浄して、N,O-ジアセチル-ニトロ体（Ⅰ-1-1; X=$CO_2Me$, Y=OAc, $R^3$=Ac) と N,O-ジアセチル-ジニトロ体（Ⅰ-1-1′; X=$CO_2Me$, Y=OAc, $R^3$=Ac) との混合物を得た。

上記混合物を DMF 250 mℓに溶解し、10% パラジウム/炭素 2 g を加え水素気流下室温で撹拌した。2 時間後、反応溶液をセライトを通しろ過し、溶媒を減圧下留去した。残渣をシリカゲルカラムクロマトグラフィー（溶出溶媒；クロロホルム）にて精製後クロロホルム-エーテル混合溶媒（以下の実施例において再結晶における 2 種もしくはそれ以上の溶媒を用いるときは混合溶媒を

意味する）で再結晶し化合物1、1.74g（30%）を mp.＞300℃の黄色針状晶として得た。また、化合物2、0.59g（10%）を mp.＞300℃の黄色粉末として得た。

化合物1： NMR(CDCℓ₃) δ；1.79(s,3H), 2.12(dd,1H,J=5.14Hz), 2.28(s,3H), 2.83(s,3H), 3.98(dd,1H,J=7.14Hz), 4.03(s,3H), 5.36(s,2H), 6.83-7.10(m,2H), 7.23-7.66(m,3H), 7.93(dd,1H,J=2.8Hz), 8.60(dd,1H,J=2.8Hz), 8.54(d,1H,J=2Hz)

MS(m/e)；567 (M+1)

化合物2： NMR(CDCℓ₃) δ；1.74(s,3H), 2.08(dd,1H,J=5.8Hz), 2.15(s,3H), 2.71(s,3H), 3.83(dd,1H,J=7.14Hz), 3.93(s,3H), 5.00(br.s,4H), 5.32(s,2H), 6.80-7.20(m,3H), 7.28(br.s,1H), 7.67(d,1H,J=8Hz), 7.70(d,1H,J=8Hz), 8.33(d,1H,J=2Hz)

MS(m/e)；582 (M+1)

実施例2

化合物1、700mg(1.22mmol)をジクロロメタン35mℓに溶解し、28%ナトリウムメチラート/メタノール溶液1.2mℓ（6.1mmol）を加え、5分後3N塩酸水溶液を加えた。溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー（クロロホルム/メタノール/DMF 80：10：10）にて精製後、クロロホルム-エーテルで再結晶を行ない、化合物3、507mg(80%)を mp.＞300℃の黄色針状晶として得た。

NMR (DMSO-d) δ；2.09(dd,1H,J=5.14Hz), 2.18(s,3H), 3.44(dd,1H,J=7.14Hz), 3.96(s,3H), 5.09(s,2H), 6.48(s,1H), 7.24(dd,1H,J=5,7Hz), 7.18-7.71(m,3H), 7.74-8.24(m,3H), 8.77(s,1H), 9.30(d,1H,J=2Hz)

MS(m/e)；483 (M+1)

実施例3

実施例2と同様の方法で、化合物2、150mg（0.26mmol）より、化合物4、53mg（41%）を mp.＞300℃の黒褐色粉末として得た。

NMR (DMSO-d) δ；1.93(dd,1H,J=5.14Hz), 2.10(s,3H), 3.36(dd,1H,J=7.14Hz), 3.94(s,3H), 4.96(br.s,2H), 6.48-7.16(m,3H), 7.24(d,1H,J=2Hz), 7.64(d,1H,J=2Hz), 7.72(d,1H,J=2Hz), 8.62(d,1H,J=2Hz)

MS(m/e)；498 (M+1)

実施例4

化合物3、155mg（0.3mmol）をメタノール3mℓおよびTHF 3mℓの混合溶媒に溶解し、35%ホルムアルデヒド水溶液を1mℓ加え、ついでシアノ水素化ホウ素ナトリウム（0.3mmol）を加え室温下1時間撹拌した。10%塩酸水を加えpH 1とした後、飽和食塩水溶液で洗浄し無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去後、残渣をシリカゲルカラムクロマトグラフィー（5%メタノール/クロロホルム）で精製し、クロロホルム-エーテル-メタノールで再結晶して、化合物5、50mg（31%）を mp.＞300℃での黒褐色粉末として得た。

NMR(DMSO-d₆) δ；2.03(dd,1H,J=5.14Hz), 2.16(s,3H), 3.20-3.50(1H), 3.40(6H), 3.93(s,3H), 5.01(d,1H,J=17), 5.07(d,1H,J=17Hz), 7.22(dd,1H,J=5.7Hz), 7.36-7.53(m,2H), 7.90-8.15(m,4H), 8.75(s,1H), 9.44(s,1H)

MS(m/e)；510 (M+)

実施例5

実施例4と同様の方法で、化合物3、140mg（0.37mmol）およびアセトアルデヒド0.17mℓより、化合物6、38mg（24%）を mp.＞300℃での黒褐色粉末として得た。

NMR(DMSO-d₆) δ；1.10(t,6H,J=7Hz), 2.10(dd,1H,J=4.3,13.3Hz), 2.15(s,3H), 3.50-3.90(m,4H), 3.93(s,3H), 5.02-5.08(m,2H), 6.42(s,1H), 7.24-7.26(m,1H), 7.39(t,1H,J=7Hz), 7.52(t,1H,J=7Hz), 7.90-8.22(m,4H), 8.75(br.s,1H), 9.40(br.s,1H)

MS(m/e)；539

実施例6

化合物1、1.8g（3.1mmol）をピリジン50mℓに溶解し、無水酢酸3mℓ（31mmol）を加え、室温下3時間撹拌した。溶媒を減圧下留去し、残渣にクロロホルムを加え5%塩酸水溶液、飽和食

塩水溶液で洗浄し、無水硫酸マグネシウムで乾燥した。残渣をシリカゲルカラムクロマトグラフィー（0.5%メタノール／クロロホルム）にて精製し、メタノール－DMF より再結晶を行ない、化合物7、1.7g（90%）を mp.＞300℃の褐色粉末として得た。

NMR(DMSO-$d_6$) $\delta$ ; 1.70(s,3H), 2.0-2.36(1H), 2.10(s,3H), 2.21(s,3H), 2.64(s,3H), 3.76-4.04(1H), 3.96(s,3H), 5.43(s,2H), 7.29(dd,1H,J=6,8Hz), 7.53(d,1H,J=8Hz), 7.63(d,1H,J=8Hz), 7.90-8.20(m,4H), 9.14(s,1H), 10.12(s,1H)

MS(m／e) ; 567 ($M^+$-Ac+1)

実施例7

実施例2と同様の方法（溶媒はDMF を用いた）で化合物7、0.7g（1.15mmol）より、化合物8、0.43g（71.3%）を mp.＞300℃（ピリジン－クロロホルム－エーテルで再結晶）の褐色針状晶を得た。

NMR (DMSO-$d_6$+$CD_3OD$) $\delta$ ; 2.13(dd,1H,J=6.14Hz), 2.18(s,3H), 2.23(s,3H), 3.52(dd,1H,J=7.14Hz), 4.02(s,3H), 5.09(s,2H), 7.12(dd,1H,J=8.7Hz), 7.36-8.20(m,6H), 9.20(s,1H)

MS(m／e) ; 524 ($M^+$)

実施例8

実施例6と同様の方法で、化合物1、100mg（0.17mmol）および、無水プロピオン酸115mg（0.88mmol）より、化合物9、50mg（47.3%）を mp.243－245℃（クロロホルム－エーテルで再結晶）の赤褐色プリズム晶として得た。

NMR (CDCl$_3$) $\delta$ ; 1.36(t,3H,J=8Hz), 1.80(s,3H), 2.09(dd,1H,J=5,14Hz), 2.22(s,3H), 2.51(q,2H,J=8Hz), 2.70(s,3H), 3.94(dd,1H,J=7,14Hz), 4.00(s,3H), 5.31(s,2H), 6.95(dd,1H,J=5,7Hz), 7.36-7.72(m,3H), 7.97(dd,1H,J=2,8Hz), 8.05(dd,1H,J=2,8Hz), 8.22(dd,1H,J=2,8Hz), 8.84(d,1H,J=2Hz)

MS(m／e) ; 566 ($M^+$-COBt+1)

実施例9

実施例2と同様の方法で、化合物9、150mg（0.24mmol）より化合物10、85mg（65.5%）を mp.＞300℃（ピリジン－クロロホルム－エーテルで再結晶）の褐色針状晶を得た。

NMR(DMSO-$d_6$) $\delta$ ; 1.16(s,3H), 2.03(dd,1H,J=5.14Hz), 2.17(s,3H), 2.40(q,2H,J=8Hz), 3.16-3.56(1H), 3.96(s,3H), 5.08(s,2H), 6.40(br.s,1H), 7.08-7.26(m,1H), 7.30-7.68(m,2H), 7.80-8.24(m,4H), 8.66(s,1H), 9.20(s,1H), 10.04(s,1H)

MS(m／e) ; 539 (M+1)

実施例10

実施例6と同様の方法で、化合物1、170mg（0.3mmol）および無水n－酪酸240mg（1.5mmol）より、化合物11、135mg（71%）を mp.113～115℃（クロロホルム－エーテルで再結晶）の褐色針状晶として得た。

NMR (CDCl$_3$) $\delta$ ; 1.10(t,3H,J=8Hz), 1.80(s,3H), 1.72-2.04(m,2H), 2.10(dd,1H,J=5,14Hz), 2.24(s,3H), 2.46(t,2H,J=8Hz), 2.76(s,3H), 3.97(dd,1H,J=7,14Hz), 4.02(s,3H), 5.36(s,3H), 6.99(dd,1H,J=5,7Hz), 7.36-7.76(m,4H), 7.92-8.36(m,3H), 8.92(s,1H)

MS(m／e) ; 637 (M+1)

実施例11

実施例2と同様の方法で、化合物11、95mg(0.15mmol）より化合物12、50mg（60.6%）を mp.294～296℃（クロロホルム再結晶）の褐色粉末として得た。

NMR(DMSO-$d_6$) $\delta$ ; 0.98(t,3H,J=8Hz), 1.48-1.84(m,2H), 2.02(dd,1H,J=5.14Hz), 2.16(s,3H), 2.36(t,2H,J=8Hz), 3.63(dd,1H,J=7.14Hz), 3.96(s,3H), 5.06(s,2H), 3.38(br.s,1H), 7.16(dd,1H,J=5.7Hz), 7.18-7.62(m,2H), 7.80-8.20(m,4H), 8.64(s,1H), 9.20(s,1H), 10.04(s,1H)

MS(m／e) ; 553 (M+1)

実施例12

化合物1、170mg（0.3mmol）をクロロホルム10mlに溶解し、トリエチルアミン0.084ml（0.6mmol）を加え、ついでイソシアン酸メチル0.88 ml（1.5mmol）を加え室温下1時間撹拌した。メタノール2 mlを加え、溶媒を減圧下留

去し、残渣をメタノールでトリチュレートして化合物（I-1-2e; X=$CO_2Me$, Y=OAc, $R^3$=Ac, $R^{4b}$= Me）150mg（80.2%）を mp.＞300℃の淡黄色粉末として得た。

MS(m/e)；593 ($M^+$-NHMe)

実施例2と同様の方法で、上記化合物1、10mg（0.17mmol）より化合物13、89mg（93.7%）を mp.＞300℃（メタノールより再結晶）の淡黄色粉末として得た。

NMR (CDCℓ$_3$+DMSO-$d_6$) δ；2.21(s,3H), 2.28(dd,1H,J=5,14Hz), 2.83(s,3H), 4.05(s,3H), 4.96(br.s,2H), 6.93(dd,1H,J=5,7Hz), 7.28-7.64(m,3H), 7.84-8.04(m,3H), 8.84(d,1H,J=2Hz)

MS(m/e)；509 ($M^+$-NHMe)

実施例13

実施例12と同様の方法で、化合物1、170mg（0.3mmol）より、化合物（I-1-2e; X=$CO_2Me$, Y=OAc, $R^3$=Ac, $R^{4b}$= Bt）139mg（73%）を淡黄色粉末として得た。

MS(m/e)；593 ($M^+$-NHBt)

実施例2と同様の方法で、上記化合物100mg（0.16mmol）より化合物14、61mg（69%）を mp.＞300℃（アセトン－水より再結晶）の淡緑色粉末として得た。

NMR (CDCℓ$_3$+$CD_3OD$) δ；1.16(t,3H,J=7.5Hz), 2.08(s,3H), 2.31(dd,1H,J=5,14Hz), 3.04-3.28(3H), 4.01(s,3H), 4.15(d,1H,J=17Hz), 4.67(d,1H,J=17Hz), 6.80(dd,1H,J=5,7Hz), 7.18-7.96(m,6H), 8.44(d,1H,J=2Hz)

MS(m/e)；($M^+$-$NH_2$Bt)

実施例14

実施例12と同様の方法で、化合物1、170mg（0.3mmol）より、化合物（I-1-2e; X=$CO_2Me$, Y=OAc, $R^3$=Ac, $R^{4b}$= Ph）172mg（83.6%）を mp.＞300℃の黄色粉末として得た。

MS(m/e)；593 ($M^+$-NHPh)

実施例2と同様の方法で、上記化合物140mg（0.2mmol）より化合物15、71mg（59%）を mp.＞300℃の淡緑色粉末として得た。

NMR (CDCℓ$_3$+$CD_3OD$) δ；2.16(s,3H), 2.27(dd,1H,J=5,14Hz), 3.20-3.52(m,1H), 4.04(s,3H), 4.67(d,1H,J=18Hz), 4.90(d,1H,J=18Hz), 6.80-8.04(m,11H), 8.75(d,1H,J=2Hz)

MS(m/e)；508 ($M^+$-$NH_2$Ph)

実施例15

化合物1、170mg（0.3mmol）をTHF 10mℓおよび酢酸1mℓの混合溶媒に溶解し、シアン酸カリウム120mg（1.5mmol）水溶液1mℓを加え、室温下1時間撹拌した。溶媒を減圧下留去し水でトリチュレートを行ない化合物（I-1-2d; X=$CO_2Me$, Y=OAc, $R^3$=Ac）178mg（97.3%）を mp.＞300℃の黄色粉末として得た。

MS(m/e)；593 ($M^+$-$NH_2$)

実施例2と同様の方法で、上記化合物80mg（0.13mmol）より化合物16、34mg（50%）を mp.＞300℃の淡黄色粉末として得た。

NMR(DMSO-$d_6$) δ；2.11(dd,1H,J=5,14Hz), 2.17(s,3H), 3.20-3.63(1H), 3.97(s,3H), 5.79(br.s,2H), 6.40(s,1H), 6.97-7.23(m,1H), 7.30-7.70(m,2H), 7.76-8.10(m,4H), 8.70(s,1H), 8.79(s,1H), 9.20(s,1H), 9.30(s,1H)

MS(m/e)；508 ($M^+$-$NH_3$)

実施例16

化合物i（Ⅲ－1；X=$CO_2Me$, Y=OAc, $R^3$=Ac）110mg（0.2mmol）をジクロロメタン10mℓに溶解し、氷冷下塩化アルミニウム133mg（1mmol）、アセチルクロライド0.015mℓ（0.2mmol）を加え、同温度にて2時間撹拌した。水10mℓを加え有機層を抽出し、飽和食塩水溶液で洗浄後無水硫酸マグネシウムで乾燥した。残渣をシリカゲルカラムクロマトグラフィー（クロロホルム）にて精製し、クロロホルム－メタノールより再結晶を行ない化合物17、60mg（50.8%）を mp.＞300℃の無色プリズム晶として得た。また、化合物18、5mg（4%）を mp.＞300℃の黄色プリズム晶として得た。

化合物17：NMR(CDCℓ$_3$) δ；1.76(s,3H), 1.09(dd,1H,5.14Hz), 2.28(s,3H), 2.52(s,3H), 2.69(s,3H), 3.93(dd,1H,J=7,14Hz), 4.01(s,3H), 5.20(s,3H), 6.89(dd,1H,J=5,7Hz), 7.28-7.72(m,

3H), 7.88-8.24(m,3H), 9.68(s,1H)

MS(m/e) ; 594 (M+1)

化合物18 : NMR(CDCℓ$_3$)δ ; 1.82(s,3H), 2.21(dd,1H,J=5.14Hz), 2.34(s,3H), 2.75(s,3H), 2.80(s,3H), 2.82(s,3H), 4.06(dd,1H,J=7.14Hz), 4.07(s,3H), 5.40(s,2H), 7.03(dd,1H,J=5,7Hz), 7.56(d,1H,J=8Hz), 8.01(d,1H,J=8Hz), 8.24(d,1H,J=8Hz), 8.25(d,1H,J=8Hz), 8.60(s,1H), 9.84(d,1H,J=2Hz)

MS(m/e) ; 636 (M+1)

実施例17

化合物i (III-1 ; X=CO$_2$Me , Y=OAc, R$^3$=Ac) 330mg (0.6mmol) をジクロロメタン30mℓに溶解し、氷冷下四塩化チタン0.46mℓ (4.2mmol) 、ジクロロメチルメチルエーテル0.11mℓ (1.2mmol) を加え、室温下3時間撹拌した。水10mℓを加え有機層を抽出し、飽和食塩水溶液で洗浄後無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去後、残渣をシリカゲルカラムクロマトグラフィー (クロロホルム) にて精製し、クロロホルム-メタノールで再結晶を行ない化合物19、130mg (37%) を mp.>300℃の無色プリズム晶として得た。また、化合物20、130mg (35.7%) を mp.>300℃の褐色粉末として得た。

化合物19 : NMR(DMSO-d$_6$)δ ; 1.72(s,3H), 2.04-2.36(m,1H), 2.25(s,3H), 2.68(s,3H), 3.80-4.08(m,1H), 4.00(s,3H), 5.43(s,2H), 7.20-8.40(m,7H), 9.60(s,1H), 10.16(s,1H),

MS(m/e) ; 580 (M+1)

化合物20 : NMR(DMSO-d$_6$)δ ; 1.72(s,3H), 2.09-2.16(m,1H), 2.29(s,3H), 2.56(s,3H), 3.80-4.08(m,1H), 4.00(s,3H), 5.08-5.44(m,2H), 7.28-7.48(m,1H), 7.88-8.32(m,4H), 8.56(s,1H), 9.40(s,1H), 10.04(s,1H), 10.25(s,1H)

MS(m/e) ; 608 (M+1)

実施例18

実施例2と同様の方法で、化合物17、50mg (0.08mmol) より、化合物21、30mg (70%) を mp.>300℃の無色針状晶として得た。

NMR(DMSO-d$_6$)δ ; 2.08(dd,1H,J=5.14Hz), 2.15(s,3H), 2.70(s,3H), 3.43(dd,1H,J=7,14Hz), 3.93(s,3H), 5.01(d,1H,J=18Hz), 5.07(d,1H,J=18Hz), 6.39(s,1H), 7.21(dd,1H,J=5,7Hz), 7.38(t,1H,J=7Hz), 7.51(t,1H,J=7Hz), 7.95(d,1H,J=8Hz), 8.01(d,1H,J=8Hz), 8.08(d,1H,J=8Hz), 8.10(d,1H,J=7Hz), 8.69(s,1H), 9.92(d,1H,J=2Hz)

MS(m/e) ; 509 (M$^+$)

実施例19

実施例2と同様の方法で、化合物19、50mg (0.086mmol) より化合物22、20mg (46.8%) を mp.>300℃の無色粉末として得た。

NMR(DMSO-d$_6$)δ ; 2.00-2.08(m,1H), 2.16(s,3H), 3.12-3.60(m,1H), 3.96(s,3H), 5.08(br.s,2H), 7.08-7.68(m,3H), 7.84-8.28(m,4H), 9.80(s,1H), 10.16(s,1H)

MS(m/e) ; 495 (M$^+$)

実施例20

実施例2と同様の方法で、化合物20、121mg (0.2mmol) より化合物23、51mg (49%) を mp.>300℃の黄色粉末として得た。

NMR(DMSO-d$_6$)δ ; 2.06(dd,1H,J=5.14Hz), 2.20(s,3H), 3.50(dd,1H,J=7.14Hz), 3.96(s,3H), 5.14(br.s,2H), 6.56(s,1H), 7.31(dd,1H,J=5.7Hz), 7.92-8.24(m,4H), 8.67(s,1H), 8.84(br.s,1H), 9.77(s,1H), 10.13(s,1H), 10.21(s,1H)

MS(m/e) ; 523 (M$^+$)

実施例21

化合物17、20mg (0.033mmol) をクロロホルムに溶解し、m-クロロ過安息香酸25mg (0.15mmol) を1時間おきに2度加え、3時間加熱還流した。飽和重ソウ水溶液、水で洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去後残渣をシリカゲルカラムクロマトグラフィー (クロロホルム) にて精製し、クロロホルム-エーテルで再結晶を行ない、化合物 (I-1-4; X=CO$_2$Me , Y=OAc, R$^3$=Ac, R$'^b$=Me) 10mg (48.0%) を mp. >300℃の褐色粉末として得た。

NMR (CDCℓ$_3$)δ ; 1.79(s,3H), 2.09(dd,1H,J=5,14Hz), 2.26(s,3H), 2.40(s,3H), 2.70(s,3H),

3.94(dd, 1H, J=7.14Hz), 4.00(s, 3H), 5.34(s, 2H), 6.98(dd, 1H, J=5, 7Hz), 7.20-7.70(m, 3H), 7.92-8.20(m, 3H), 8.90(d, 1H, J=2Hz)

MS(m/e) ; 610 (M+1)

実施例2と同様の方法で、上記化合物1.0g (1.6mmol) より化合物24、0.3 (38.8%) をmp. >300℃ (クロロホルムより再結晶) の赤褐色プリズム晶として得た。

NMR(DMSO-$d_6$) $\delta$ ; 1.97(dd, 1H, J=5, 14Hz), 2.12 (s, 3H), 3.35(dd, 1H, J=7, 14Hz), 3.92(s, 3H), 5.01(s, 2H), 6.32(s, 1H), 6.88-7.16(m, 2H), 7.28-7.64(m, 2H), 7.72(d, 1H, J=8Hz), 7.80-8.20 (m, 2H), 8.60(s, 1H), 8.71(d, 1H, J=2Hz), 9.10 (s, 1H)

MS(m/e) ; 481 (M+1)

実施例22

実施例21と同様の方法で化合物20、182mg (0.3mmol) より化合物 (I-1-4' ; X=$CO_2Me$, Y=OAc, $R^a$=Ac, $R'^b$=H) 80mg (42%) を褐色粉末として得た。

NMR (CDCl$_3$) $\delta$ ; 1.84(s, 3H), 1.96-2.40(m, 1H), 2.28(s, 3H), 2.76(s, 3H), 3.84-4.12(m, 1H), 4.02(s, 3H), 5.36(s, 2H), 6.72-7.08(m, 1H), 7.24-7.64(m, 3H), 7.76-8.08(m, 2H), 8.48(s, 2H), 9.01(d, 1H, J=2Hz)

実施例2と同様の方法で、上記化合物80mg (0.13mmol) より化合物25 10mg (15%) をmp. >300℃の黄色粉末として得た。

NMR(DMSO-$d_6$) $\delta$ ; 1.97(dd, 1H, J=5, 14Hz), 2.10 (s, 3H), 3.00-3.50(1H), 3.92(s, 3H), 4.94(s, 2H), 6.23(s, 1H), 6.80-7.12(m, 3H), 7.35(d, 1H, J=2Hz), 7.65(d, 1H, J=8Hz), 7.76(d, 1H, J=8Hz), 8.46(s, 1H), 8.67(d, 1H, J=2Hz), 9.03(s, 1H), 9.20(s, 1H)

MS(m/e) ; 500 (M+1)

実施例23

DMF 1mlに50%水素化ナトリウム38.4mg (0.8mmol) を懸濁させ、氷冷下化合物24、96mg (0.2mmol) のDMF溶液2 mlを加える。20分後同温度にてヨウ化メチル0.013 ml (0.2mmol) を加え1時間撹拌した。反応終了後、飽和塩化アンモニウム溶液を加え、クロロホルム抽出し、飽和食塩水で洗浄し無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー (クロロホルム) にて精製し、ジクロロメタン-メタノールより再結晶を行ない、化合物26、45mg (45.3%) をmp. 293-294℃の褐色針状晶として得た。

NMR (CDCl$_3$+DMSO-$d_6$) $\delta$ ; 2.05(dd, 1H, J=5, 14Hz), 2.16(s, 3H), 3.00-3.50(1H), 3.92(s, 3H), 3.96 (s, 3H), 5.03(br. s, 2H), 6.96-8.12(m, 6H), 8.54 (br. s, 1H), 8.92(d, 1H, J=2Hz)

MS(m/e) ; 498 (M+1)

実施例24

実施例23と同様の方法で、化合物24、96mg (0.2mmol) およびヨウ化エチルより化合物27、75mg (73.5%) をmp. 283-286℃ (クロロホルムにより再結晶) の黄色針状晶として得た。

NMR(DMSO-$d_6$) $\delta$ ; 1.46(t, 3H, J=7Hz), 2.03(dd, 1H, J=5, 14Hz), 2.18(s, 3H), 3.96(s, 3H), 4.20(q, 2H, J=7Hz), 5.07(s, 2H), 6.36(s, 1H), 7.07-7.28 (m, 2H), 7.32-7.68(m, 2H), 7.80-8.20(m, 3H), 8.64(s, 1H), 8.91(d, 1H, J=2Hz)

MS(m/e) ; 512 (M+1)

実施例25

実施例23と同様の方法で、化合物24、96mg (0.2mmol) および1-ヨードプロパンより化合物28、60mg (57.1%) をmp. 228-230℃ (クロロホルムにより再結晶) の褐色針状晶として得た。

NMR(DMSO-$d_6$) $\delta$ ; 1.07(t, 3H, J=8Hz), 1.72-2.24 (m, 3H), 2.16(s, 3H), 2.90-3.40(1H), 3.94(s, 3H), 4.08(t, 2H, J=7Hz), 5.04(br. s, 2H), 6.34(s, 1H), 7.00-7.24(m, 2H), 7.32-7.60(m, 2H), 7.76-8.16 (m, 3H), 8.60(s, 1H), 8.87(d, 1H, J=2Hz)

MS(m/e) ; 526 (M+1)

実施例26

実施例23と同様の方法で、化合物24、96mg (0.2mmol) および2-ヨードプロパンより化合物29、40mg (38%) を mp. 213-214.5

で（クロロホルムにより再結晶）の黄褐色プリズム晶を得た。

NMR(DMSO-$d_6$) $\delta$ ; 1.35(d,6H,J=7Hz), 1.99(dd,1H,J=5.14Hz), 2.14(s,3H), 3.00-3.52(1H), 3.92(s,3H), 4.48-4.80(m,1H), 5.02(br.s,2H), 6.32(br.s,1H), 7.00-7.24(m,2H), 7.32-9.64(m,2H), 7.72-8.20(m,3H), 8.60(br.s,1H), 8.87(d,1H,J=2Hz)

MS(m/e) ; 526 (M+1)

実施例27

実施例23と同様の方法で、化合物24、96 mg (0.2 mmol) および1-ヨードブタンより化合物30、35 mg (32.5%) をmp. 166-168℃（クロロホルムにより再結晶）の黄褐色プリズム晶として得た。

NMR(DMSO-$d_6$) $\delta$ ; 0.99(t,3H,J=7Hz), 1.32-2.24(m,5H), 2.16(s,3H), 3.16-3.52(1H), 3.93(s,3H), 4.12(t,2H,J=8Hz), 5.03(br.s,2H), 6.33(s,1H), 7.04-7.28(m,2H), 7.28-7.68(m,2H), 7.70-8.20(m,3H), 8.60(s,1H), 8.89(d,1H,J=2Hz)

MS(m/e) ; 540 (M+1)

実施例28

化合物19、2.51 g (4.3 mmol) をメタノール20 mlおよびクロロホルム100 mlの混合溶媒に溶解し、氷冷下水素化ホウ素ナトリウム488 mg (12.4 mmol) を加え、同温度にて30分撹拌した。3N塩酸水溶液を加えpH2とし、有機層を抽出し、飽和重ソウ水溶液、飽和食塩水溶液で順次洗浄して無水硫酸マグネシウムで乾燥した。残渣をエーテルでトリチュレートし、化合物31、1.8 g (72%) をmp. 270-277℃の淡黄色粉末として得た。

NMR (CDCl$_3$+CD$_3$OD) $\delta$ ; 1.80(s,3H), 2.11(dd,1H,J=5.14Hz), 2.26(s,3H), 2.64(s,3H), 3.93(dd,1H,J=7,14Hz), 4.03(s,3H), 4.86(s,2H), 5.22(s,2H), 6.99(dd,1H,J=5,7Hz), 7.40-7.72(m,4H), 7.80-8.08(m,2H), 9.04(s,1H)

MS(m/e) ; 581 (M$^+$)

実施例29

化合物31、500 mg (0.88 mmol) をクロロホルム30 mlに溶解し、エタンチオール0.64 ml (8.6 mmol) およびカンファースルホン酸199 mg (0.86 mmol) を加え室温下2時間撹拌した。反応液を飽和重ソウ水溶液、飽和食塩水溶液で順次洗浄し、無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー（5%酢酸エチル-トルエン）に付し、化合物32、340 mg (63%) をmp. 181-184℃の無色プリズム晶として得た。

NMR (CDCl$_3$) $\delta$ ; 1.28(t,3H,J=8Hz), 1.76(s,3H), 2.11(dd,1H,J=5.14Hz), 2.26(s,3H), 2.53(q,2H,J=8Hz), 2.80(s,3H), 3.97(dd,1H,J=7,14Hz), 4.00(s,2H), 4.01(s,3H), 5.36(s,2H), 7.02(dd,1H,J=5,7Hz), 7.14-7.80(m,4H), 7.92-8.20(m,2H), 9.13(s,1H)

MS(m/e) ; 626 (M$^+$)

実施例30

化合物32、125 mg (0.2 mmol) を酢酸エチルに溶解しラネーニッケル200 mgを加え、7時間加熱還流した。反応溶液をセライトを通しろ過し、溶媒を減圧下留去し、化合物33、116 mg (100%) を淡黄色粉末として得た。

NMR (CDCl$_3$) $\delta$ ; 1.75(s,3H), 2.04(dd,1H,J=5.14Hz), 2.20(s,3H), 2.48(s,3H), 2.61(s,3H), 3.86(dd,1H,J=7.14Hz), 3.99(s,3H), 5.08(s,2H), 6.91(dd,1H,J=5,7Hz), 7.16-7.64(m,4H), 7.80-8.04(m,2H), 8.80(s,1H)

MS(m/e) ; 566 (M$^+$)

実施例31

実施例2と同様の方法で、化合物32、80 mg (0.12 mmol) より化合物34、50 mg (77%) をmp. > 300℃の無色プリズム晶として得た。

NMR (CDCl$_3$) $\delta$ ; 1.30(t,3H,J=8Hz), 2.12(s,3H), 2.54(q,2H,J=8Hz), 2.97(dd,1H,J=5.14Hz), 3.63(dd,1H,J=7.14Hz), 3.80(s,2H), 4.08(s,3H), 4.37(d,1H,J=18Hz), 4.59(d,1H,J=18Hz), 5.28(s,1H), 5.56(s,1H), 6.79(dd,1H,J=5,7Hz), 7.12-7.70(m,4H), 7.80-8.12(m,2H), 8.60(s,1H)

MS(m/e) ; 540 (M$^+$-1)

実施例32

実施例２と同様の方法で、化合物33、１００mg（0.１７mmol）より、化合物35、７０mg（８２%）をmp.＞３００℃の淡黄色粉末として得た。

NMR（CDCℓ₃）δ：2.12(s,3H)，2.38(s,3H)，2.95(dd,1H,J=5,14Hz)，3.48(dd,1H,J=7,14Hz)，4.04(s,3H)，4.24(d,1H,J=18Hz)，2.48(d,1H,J=18Hz)，5.42(s,1H)，5.75(s,1H)，6.78(dd,1H,J=5,7Hz)，6.94-7.20(m,2H)，7.28-7.62(m,2H)，7.81(dd,1H,J=2,8Hz)，8.00(d,1H,J=8Hz)，8.40(s,1H)

MS(m／e)：４８１（M⁺）

実施例３３

化合物34、９０mg(0.１６６mmol)をクロロホルム５mℓに溶解し、m－クロロ過安息香酸２９mg（0.１６６mmol）を加え、遮光下室温で２時間撹拌した。反応溶液を飽和重ソウ水溶液、飽和食塩水溶液で順次洗浄し無水硫酸マグネシウムで乾燥した。残渣をシリカゲルカラムクロマトグラフィー（２%メタノール／クロロホルム）にて精製し、化合物36、６０mg（６５%）をmp.＞３００℃の淡黄色粉末として得た。

NMR(DMSO-d₆)δ：1.25(t,3H,J=7Hz)，2.03(dd,1H,J=5,14Hz)，2.15(s,3H)，2.64-2.86(m,2H)，3.36-3.41(m,1H)，3.92(s,3H)，4.11(d,1H,J=13Hz)，4.28(d,1H,J=13Hz)，4.97(d,1H,J=18Hz)，5.03(d,1H,J=18Hz)，7.13(dd,1H,J=5,7Hz)，7.36(t,1H,J=7Hz)，7.44(dd,1H,J=1,8Hz)，7.48(d,t,1H,J=1,8Hz)，7.90(d,1H,J=8Hz)，7.94(d,1H,J=8Hz)，8.62(s,1H)，9.15(s,1H)

MS(m／e)：４８０（M⁺-S(O)Bt）

実施例３４

K２５２、９３mg（0.２mmol）をピリジン３mℓに溶解し、氷冷下臭素0.０２４mℓ（0.４８mmol）を加え一晩撹拌した。反応終了後、反応溶液にＴＨＦを加え、５%チオ硫酸ナトリウム水溶液、飽和食塩水で順次洗浄し、無水硫酸マグネシウム乾燥後溶媒を減圧下留去した。残渣をＴＨＦおよびメタノールにより再結晶を行ない、化合物37、７０mg（６４%）をmp.２５１～２５２℃の黄褐色粉末として得た。

NMR(CDCℓ₃－DMSO-d₆)δ：1.96-2.30(m,1H)，2.20(s,3H)，3.12-3.60(m,1H)，4.00(s,3H)，5.04(s,2H)，6.36(s,1H)，7.04-7.24(m,1H)，7.36-8.22(m,6H)，8.64(br.s,1H)，9.48(br.s,1H)

MS(m／e)：５４７（M⁺）

実施例３５

参考例４で得られる化合物ｄ３００mg(0.６mmol)をTHF９０mℓおよび水１０mℓの混合溶媒に溶解し、メチルヒドラジン0.３２mℓ（６mmol）を加え室温下１日撹拌した。反応溶液を飽和食塩水溶液で洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー（１%メタノール／クロロホルム）にて精製し、化合物38、１２６mg(４０%)を黄褐色粉末として得た。

NMR(DMSO-d₆)δ：1.92-2.36(1H)，2.03(s,3H)，2.23(s,3H)，3.08-3.60(1H)，3.12(s,3H)，5.00(s,3H)，6.92-7.16(m,1H)，7.20-7.60(m,4H)，7.72-8.28(m,3H)，9.24(d,1H,J=8Hz)

MS(m／e)：５２４（M+1）

実施例３６

参考例４で得られる化合物ｄ３００mg(0.６mmol)およびグリシンメチルエステル塩酸塩７５３mg（６mmol）をTHF９０mℓおよび水１０mℓの混合溶媒に溶解し、トリエチルアミン0.８４mℓを加え室温下１日撹拌した。反応溶液を飽和食塩水溶液で洗浄し無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去後、残渣をシリカゲルカラムクロマトグラフィー（１%メタノール／クロロホルム）にて精製し、化合物39、８７mg(２６%)を黄褐色粉末として得た。

NMR（CDCℓ₃）δ：1.72(s,3H)，1.92-2.50(1H)，2.40(s,3H)，3.68-4.52(m,3H)，3.82(s,3H)，5.02(br.s,2H)，6.96-8.20(m,8H)，9.31(d,1H,J=8Hz)

MS(m／e)：５６６（M⁺）

実施例３７

実施例３６と同様の方法で、参考例４で得られる化合物ｄ５００mg（0.９７mmol）およびＬ－プロリンベンジルエステル塩酸塩2.２７g(9.７mmol)

より、化合物40、１９５mg（２９%）をmp. 202－２０５℃の無色粉末として得た。

NMR (CDCℓ₃) δ ; 1.52(s, 3H), 1.80-2.50(m, 5H), 2.36(s, 3H), 3.08-3.52(m, 2H), 3.84-4.30(m, 2H), 4.64(s, 2H), 5.14(d, 1H, J=13Hz), 5.31(d, 1H, J=13Hz), 6.98(dd, 1H, J=5, 14Hz), 7.16-7.60(m, 5H), 7.70-7.96(m, 2H), 9.32(d, 1H, J=8Hz)

MS(m/e) ; ６８３ (M⁺)

実施例３８

化合物40、１３２mg（0.2mmol）をDMF 5 mℓに溶解し、１０%パラジウム／炭素５０mgを加え、水素気流下４０℃で3.5時間撹拌した。反応溶液をセライトを通しろ過し、溶媒を減圧下留去した。残渣をシリカゲルカラムクロマトグラフィー（クロロホルム／メタノール／２８%アンモニア水 ９０：１０：0.5）にて精製し、化合物41、８０mg(67 %) を mp.＞３００℃の淡黄色粉末として得た。

NMR(DMSO-d₆) δ ; 1.66(s, 3H), 1.88-2.36(m, 5H), 2.49(s, 3H), 3.20-3.60(m, 2H), 3.95(dd, 1H, J=7, 14Hz), 4.12-4.50(m, 1H), 5.04(s, 2H), 7.00-7.70(m, 5H), 7.86(dd, 1H, J=2, 8Hz), 8.00-8.24(m, 2H), 8.61(s, 1H), 9.23(d, 1H, J=8Hz)

MS(m/e) ; ５９３ (M+1)

実施例３９

化合物39、８７mg（0.15mmol）をTHF 5mℓに溶解し、２N水酸化ナトリウム水溶液0.24 mℓ（0.68mmol）を加え室温下2時間撹拌した。３N塩酸水溶液を加え pH 2となし、飽和食塩水溶液で洗浄し、無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去後、残渣をシリカゲルカラムクロマトグラフィー（クロロホルム／メタノール／28%アンモニア水：９０／１０／５）にて精製し、化合物42、２７mg（３５%）をmp.＞３００℃の無色粉末として得た。

NMR(DMSO-d₆) δ ; 1.96-2.36(m, 1H), 2.20(s, 3H), 3.08-3.50(1H), 3.88-4.04(m, 2H), 5.03(br. s, 2H), 6.53(s, 1H), 6.90-8.24(m, 6H), 8.52-8.80(m, 2H), 9.26(d, 1H, J=8Hz)

MS(m/e) ; ５１１ (M+1)

実施例４０

K２５２、4.67g（10mmol）をTHF４００mℓに溶解し、－２０℃にて水素化リチウムアルミニウム0.38g（１０mmol）のTHF 溶液５０ mℓを加え、同温度にて１時間撹拌した。３N塩酸水溶液を加え pH 2とし、セライトを通しろ過後、ろ液を飽和食塩水溶液で洗浄し無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去後残渣をシリカゲルカラムクロマトグラフィー（クロロホルム）にて精製し、化合物43、1.56g（３５.７%）をmp.＞３００℃の淡黄色粉末として得た。

NMR (CDCℓ₃+DMSO-d₆) δ ; 2.04-2.48(m, 1H), 2.24(s, 3H), 3.08-3.76(1H), 4.90(br. s, 2H), 6.91(dd, 1H, J=5, 7Hz), 7.08-7.60(m, 5H), 7.76-8.08(m, 2H), 9.19(d, 1H, J=8Hz), 10.10(s, 1H)

MS(m/e) ; ４３７ (M⁺)

実施例４１

化合物43、１００mg（0.23mmol）をTHF 5mℓおよび水0.5 mℓに溶解し、ヒドロキシルアミン塩酸塩７９mg（1.1mmol）を加え１日撹拌した。溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー（１%メタノール／クロロホルム）にて精製し、化合物44、８５mg（８２%）をmp.２４５－２５６℃の淡黄色粉末として得た。

NMR(DMSO-d₆) δ ; 1.98-2.30(m, 1H), 2.20(s, 3H), 3.16-3.70(m, 1H), 5.03(s, 2H), 6.84-7.08(m, 1H), 7.16-8.20(m, 8H), 8.58(s, 1H), 9.26(d, 1H, J=8Hz)

MS(m/e) ; ４５２ (M⁺)

実施例４２

実施例４１と同様の方法で、化合物43、１００mg（0.23mmol）およびセミカルバジド塩酸塩128 mg（1.1mmol）より、化合物45、７５mg（６６%）を mp.＞３００℃の黄褐色粉末として得た。

NMR(DMSO-d₆) δ ; 1.90-2.36(1H), 2.08(s, 3H), 3.00-3.60(1H), 5.00(s, 2H), 6.96-8.20(m, 8H), 8.56(br. s, 1H), 9.22(d, 1H, J=8Hz)

MS(m/e) ; ４９５ (M+1)

実施例４３

実施例４１と同様の方法で、化合物43、８７mg（0.2mmol）およびアミノグアニジン硫酸塩264

mg（1.0 mmol）より、化合物46、60 mg（60%）をmp.＞300℃の淡黄色粉末として得た。

NMR(DMSO-$d_6$) δ：1.96-2.30(m,1H), 2.15(s,3H), 3.04-3.64(m,1H), 5.02(br.s,1H), 6.44(s,1H), 7.00-8.20(m,8H), 8.60(s,1H), 9.22(d,1H,J=8Hz)

MS(m/e)：494 (M+1)

実施例44

実施例41と同様の方法で、化合物43、87 mg（0.2 mmol）および2-ヒドラジノ-2-イミダゾリン臭化水素酸塩181 mg（1.0 mmol）より、化合物47、55 mg（53%）をmp.＞300℃の淡黄色粉末として得た。

NMR(DMSO-$d_6$) δ：1.68-2.30(m,1H), 2.08(s,3H), 3.00-3.70(1H), 5.00(s,2H), 5.96(s,1H), 7.00-8.12(m,8H), 8.56(s,1H), 9.21(d,1H,J=8Hz)

MS(m/e)：520 (M+1)

実施例45

実施例23と同様の方法でK252、184 mg（0.4 mmol）およびヨウ化メチルより、化合物48、38 mg（20%）をmp. 300-302℃の無色プリズム晶として得た。

NMR (CDCl$_3$) δ：2.23(dd,1H,J=6,13Hz), 2.20(s,3H), 3.12(s,3H), 3.28-3.48(m,1H), 3.37(s,3H), 4.04(s,3H), 5.00(s,2H), 7.03(dd,1H,J=6,8Hz), 7.28-7.64(m,5H), 7.88-8.08(m,2H), 9.46(br.d,1H,J=8Hz)

MS(m/e)：495 (M$^+$)

実施例46

K252、467 mg（1 mmol）をクロロホルム20 mlに溶解し、N-クロロコハク酸イミド133 mg（1 mmol）およびAIBN 164 mg（1 mmol）を加え、3時間加熱還流した。溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー（クロロホルム）にて精製し、化合物49、229mg(46%)をmp.125 -129 ℃の淡黄色粉末として得た。

NMR (CDCl$_3$) δ：2.20(s,3H), 2.68(dd,1H,J=5.14Hz), 3.43(dd,1H,J=7,14Hz), 4.12(s,3H), 4.88(d,1H,J=15Hz), 5.04(d,1H,J=15Hz), 6.87(dd,1H,J=5,7Hz), 7.24-7.64(m,5H), 7.84-8.00(m,2H), 9.00(d,1H,J=8Hz)

MS(m/e)：501 (M$^+$)

実施例47

参考例8で得られる化合物h 120 mg（0.27 mmol）をDMF 5 mlに溶解し、氷冷下チオカルボニルジイミダゾール98 mg（0.55 mmol）を加え同温度にて1時間撹拌した。反応溶液にTHF 30 mlを加え飽和食塩水溶液で洗浄し無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去し、化合物50、120 mg（93%）をmp.＞300℃の淡黄色粉末として得た。

NMR(DMSO-$d_6$) δ：2.10-2.64(m,1H), 2.32(s,3H), 3.00-3.52(m,1H), 4.05(d,1H,J=11Hz), 4.38(d,1H,J=11Hz), 5.02(s,2H), 6.96-8.16(m,7H), 8.60(s,1H), 9.21(d,1H,J=8Hz)

MS(m/e)：481 (M+1)

実施例48

化合物50、88 mg（0.18 mmol）をDMF 2 mlに溶解し、ヨウ化メチル0.1 mlを加え室温下2.5時間撹拌した。溶媒を減圧下留去後、残渣をシリカゲルカラムクロマトグラフィー（クロロホルム）にて精製し、化合物51、14 mg（15.7%）をmp.223-225℃の黄色粉末として得た。

NMR(DMSO-$d_6$) δ：2.08-2.44(m,1H), 2.24(s,3H), 2.30(s,3H), 3.20(dd,1H,J=7,14Hz), 4.06(d,1H,J=14Hz), 4.57(d,1H,J=14Hz), 5.02(s,2H), 7.12-8.20(m,7H), 8.63(s,1H), 9.24(d,1H,J=8Hz)

MS(m/e)：494 (M$^+$)

実施例49

参考例5で得られる化合物e 87 mg（0.2 mmol）をクロロホルム5 mlに溶解し、2,2-ジメトキシプロパン104 mg（1 mmol）およびカンファースルホン酸10 mgを加え、2時間加熱還流した。反応溶液を飽和重ソウ水溶液、飽和食塩水溶液で順次洗浄し無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去後、残渣をシリカゲルカラムクロマトグラフィー（1%メタノール/クロロホルム）にて精製し、化合物52、68 mg（71.5%）をmp.278-280℃の黄褐色粉末として得た。

NMR (CDCl$_3$) δ：1.14(s,3H), 1.40(s,3H),

2.24(s,3H), 2.41(dd,1H,J=5,14Hz), 2.82(dd,1H,J=5,14Hz), 4.05(d,1H,J=10Hz), 4.49(d,1H,J=10Hz), 4.96(s,2H), 6.68(dd,1H,J=5,7Hz), 7.24-8.20(m,7H), 9.40-9.60(m,1H)

MS(m/e)；479(M⁺)

実施例50

K252、467mg(1mmol)をアセトニトリル10mlに溶解し、ついでテトラフルオロホウ酸ニトロニウム133mg(1mmol)を加え3時間室温撹拌した。溶媒を減圧下留去し、残渣をシリカゲルクロマトグラフィー(5%DMP/クロロホルム)にて精製後、化合物53、50mg(10%)をmp.>300℃の黄色粉末として得た。

NMR(DMSO-$d_6$)δ；2.12(dd,1H,J=5,14Hz),2.16(s,3H), 3.45(dd,1H,J=7.4,14Hz), 3.94(s,3H), 4.99(d,1H,18Hz), 5.06(d,1H,18Hz), 6.44(s,1H), 7.26(dd,1H,J=5,7.4Hz), 7.39(t,1H,J=8Hz), 7.53(t,1H,7Hz), 7.96(d,1H,8Hz), 8.08(t,2H,J=8Hz), 8.31(dd,1H,J=2.4,7Hz), 8.77(s,1H), 10.09(d,1H,J=2Hz)

MS(m/e)；512(M⁺)

実施例51

K-252、93mg(0.2mmol)をTHP5mlに溶解し、氷冷下クロロスルホニルイソシアネート0.17ml(2mmol)を加え、同温度にて2時間撹拌した。ついで水1mlを加え70℃にて1時間撹拌後、反応溶液を飽和重ソウ水溶液、飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー(2%メタノール/クロロホルム)で精製し、化合物54、85mg(77%)をmp. 280-285℃の無色粉末として得た。

NMR(DMSO-$d_6$)δ；2.17(dd,1H,J=5,14Hz),2.18(s,3H), 3.92(dd,1H,J=7,14Hz), 3.94(s,3H), 5.28(d,1H,18Hz), 5.34(d,1H,18Hz), 7.22(dd,1H,J=5,7Hz), 7.32(t,1H,J=7Hz), 7.42(t,1H,J=7Hz), 7.50～7.58(m,2H), 7.95～8.01(m,3H), 9.06(d,1H,J=8Hz)

MS(m/e)；554(M+1)

実施例52

参考例5で得られる化合物e、43.9mg(0.1mmol)をDMF1mlに溶解し、N-ベンジルオキシカルボニルグリシン無水物40mg(0.1mmol)およびトリエチルアミン0.016ml(0.12mmol)を加え100℃で1時間撹拌した。反応溶液を飽和食塩水で洗浄し無水硫酸マグネシウムで乾燥後溶媒を減圧下留去した。残渣をシリカゲルカラムクロマトグラフィー(2%メタノール/クロロホルム)にて精製し、化合物55、30mg(48%)を得た。

NMR(CDCl₃)δ；2.01(s,3H), 2.80-3.40(m,2H), 3.92-4.80(m,6H), 5.04(s,2H), 5.40-5.80(m,3H), 6.50(m,1H), 6.80-7.62(m,10H), 7.76(d,1H,J=8Hz), 7.98(d,1H,J=8Hz), 8.58(d,1H, J=8Hz)

MS(m/e)；631(M+1)⁺

実施例53

化合物55、60mg(0.095mmol)をDMF1ml、エタノール10mlに溶解し、1N塩酸0.15ml、10%パラジウム/炭素60mgを加え、水素気流下40℃で10分間撹拌した。反応溶液をセライトを通しろ過した後ろ液に水15mlを加えた。エタノールを減圧下留去した後凍結乾燥を行い、化合物56、23mg(49%)を得た。

NMR(DMSO-$d_6$)δ；2.00-2.40(m,1H), 2.24(s,3H), 3.00-3.60(m,1H), 4.03(s,2H), 4.61(m,2H), 5.03(br.s,2H), 6.00(s,1H), 7.00-8.16(m,8H), 8.60(br.s,1H), 9.22(d,1H,J=8Hz)

MS(m/e)；497(M+1)⁺

実施例54

参考例5で得られる化合物e、439mg(1mmol)をクロロホルム20mlに溶解し、トリ-O-アセチル-D-グルカール、1.36g(5mmol)およびNBS、623mg(3.5mmol)を加え室温遮光下8時間撹拌した。反応溶液を1Nチオ硫酸ナトリウム、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を減圧下留去した。残渣をシリカゲルカラムクロマトグラフィー(1%メタノール/クロロホルム)にて精製しグリコシド体(XXI；Y=OH, $R_1$=$R_2$=$R_3$=H, $M_1$=Ac)360mg(46%)を得た。

MS(m/e)；790(M+1)⁺，792(M+1)⁺

上記グリコシド体、280mg(0.35mmol)をトルエン20mlに懸濁させ、AIBN 60mg(0.35mmol)および水素化トリブチル錫0.49ml(175mmol)を加え60℃で1時間撹拌した。反応溶液に酢酸エチルを加え飽和食塩水で洗浄し無水硫酸マグネシウムで乾燥後溶媒を減圧下留去した。残渣をシリカゲルカラムクロマトグラフィー(0.5%メタノール/クロロホルム)にて精製し、化合物57、70mg(28%)を得た。

NMR(DMSO-$d_6$) $\delta$；1.75-1.83(m,1H), 1.95-1.99(m,1H), 2.00(s,3H), 2.03(s,3H), 2.04(s,3H), 2.15(s,3H), 2.40-2.44(m,1H), 3.10(dd,1H,J=7.5,13.5Hz), 3.84(d,1H,J=10Hz), 3.89-3.93(m,1H), 4.07-4.11 (m,2H), 4.19(d,1H,J=10Hz), 4.26-4.30(m,2H), 4.88-5.18 (m,5H), 5.64(s,1H), 7.00(dd,1H,J=5.5, 7.5Hz), 7.25-7.49(m,4H), 7.80(d,1H,J=8.4Hz), 7.97(d,1H,J=8.4Hz), 8.04(d,1H,J=7.7Hz), 8.6 (s,1H), 9.19(d,1H,J=8Hz)

MS(m/e)；712(M+1)⁺

実施例56

参考例10で得られる化合物j、421mg(0.1mmol)をDMF 1mlに溶解し、β-D-チオグルコースナトリウム塩32.7mg(0.15mmol)を加え、50℃で2時間撹拌した。溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー(クロロホルム/メタノール/28%アンモニア水＝9/1/0.1)にて精製し、化合物59、38mg(62%)を得た。

NMR(DMSO-$d_6$) $\delta$；2.01(dd, 1H,J=5,13.6Hz), 2.16(s,3H), 3.04-3.79(m,9H), 4.46(d,1H,J=9.5Hz), 4.70(br.t,J=5.5Hz), 4.96(d,1H,J=18Hz), 5.03(d,1H,J=18Hz), 5.10(br.s,1H), 5.31(d,1H,J=5.3Hz), 5.63(s,1H), 7.03(m,1H), 7.27-7.49(m,4H), 7.83(d,1H,J=8.4Hz), 7.99-8.05(m,2H), 8.60(s,1H), 9.19(d,1H,J=7.9Hz)

MS(m/e)；618(M+1)⁺

実施例57

K252、467mg(1mmol)をクロロホルム5mlに溶解し、モレキュラーシーブ4A 500mgおよびクロロスルホン酸0.14ml(2mmol)を氷冷下加え、同温度にて3時間撹拌した。反応溶液に水2mlを加え溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー(クロロホルム/メタノール/28%アンモニア水＝80/20/5)にて精製し、化合物60、142mg(26%)を得た。

NMR(DMSO-$d_6$+$D_2O$) $\delta$；2.01(dd,1H,J=5,13Hz), 2.14(s,3H), 3.14-3.60(m,1H), 3.90(s,3H), 4.98(br.s,2H), 7.00-8.12(m,6H), 9.40(s,1H)

MS(m/e)；548(M+1)⁺

実施例58

化合物60、110mg(0.2mmol)に五塩化リン83mg(0.4mmol)およびオキシ塩化リン0.19ml(2mmol)を加え、1.5時間加熱還流した。反応溶液に水10mlとTHF 10mlを加え、有機層を分取し、飽和食塩水で洗浄後無水硫酸マグネシウムで乾燥し溶媒を減圧下留去した。残渣をシリカゲルカラムクロマトグラフィー(1%メタノール/クロロホルム)にて粗精製し、スルホニルクロ

ライド体（X；X=$CO_2Me$, Y=OH, $R^3$=H）50mgを得た。これをDMF 2mlに溶解し、ピリジン0.079ml（0.5mmol）およびN－メチルピペラジン0.05mlを加え室温下2時間攪拌した。溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー（2.5%メタノール／クロロホルム）にて精製し、化合物61、10mg（8%）を得た。

NMR(DMSO-$d_6$) $\delta$ ：2.07-2.18(m,1H), 2.12(s,3H), 2.15(s,3H), 2.44(m,4H), 2.96(m,4H), 3.20-3.50(m,1H), 3.93(s,3H), 5.02(d,1H,J=18Hz), 5.08(d,1H,J=18Hz), 6.41(s,1H), 7.25(dd,1H,J=5.7Hz), 7.37-8.17(m,7H), 8.69(s,1H), 9.70(d,1H,J=2Hz)

MS(m／e)；630 (M+1)$^+$

実施例59

実施例21で得られる化合物24、48.3mg（0.1mmol）をTHF 2mlに溶解し、クロロギ酸p－ニトロフェニル36mg（0.18mmol）およびトリエチルアミン0.033ml（0.24mmol）を加え、室温下1日攪拌した。反応溶液を飽和食塩水で洗浄し無水硫酸マグネシウムで乾燥後、溶媒を減圧下留去した。残渣をシリカゲルカラムクロマトグラフィー（1%メタノール／クロロホルム）にて精製し、化合物62、66mg（100%）を得た。

NMR(CDCl$_3$) $\delta$ ：2.00(s,3H), 2.62(dd,1H,J=5.14Hz), 3.34(dd,1H,J=7.14Hz), 4.00(s,3H), 4.14(d,1H,J=18Hz), 4.36(d,1H,J=18Hz), 5.72(s,1H), 6.68(dd,1H,J=5.7Hz), 6.80-8.40(m,6H), 8.64 (s,1H), 9.68(br.s,1H)

MS(m／e)；649 (M+1)$^+$

実施例60

化合物62、60mg（0.074mmol）をDMF 2mlに溶解し、N－イソプロピル－1－ピペラジンアセトアミド16.4mg（0.088mmol）を加え、室温下1時間攪拌した。反応溶液にTHF 10mlを加え、飽和重曹水、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を減圧下留去した。残渣をシリカゲルカラムクロマトグラフィー（4%メタノール／クロロホルム）で精製し、化合物63、42mg（82%）を得た。

NMR(CDCl$_3$) $\delta$ ：1.20(d,6H,J=8Hz), 2.00(s,3H), 2.40-2.80(m,5H), 3.00(s,2H), 3.25(dd,1H,J=7.14Hz), 3.68-4.16(m,5H), 4.00(s,3H), 4.29(d,1H,J=18Hz), 4.53(d,1H,J=18Hz), 5.36(br.s,1H), 5.56(s,1H), 6.68(dd,1H,J=5.7Hz), 6.80-8.04(m,7H), 8.56(br.s,1H)

MS(m／e)；695 (M+1)$^+$

実施例61

実施例28で得られる化合物31、245mg（0.42mmol）をクロロホルム20mlに溶解し、エタノール20ml、カンファースルホン酸98mg（0.42mmol）を加え、6時間加熱還流した。溶媒を減圧下留去し、残渣にクロロホルム20mlを加え、飽和重曹水、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を減圧下留去した。残渣をシリカゲルカラムクロマトグラフィー（1%メタノール／クロロホルム）にて精製し、化合物64、143mg（56%）を得た。

NMR(CDCl$_3$) $\delta$ ：1.30(t,3H,J=7.5Hz), 1.80(s,3H), 2.13(dd,1H,J=5.14Hz), 2.28(s,3H), 2.80(s,3H), 3.65(q,2H,J=7.5Hz), 3.97(dd,1H,J=7.14Hz), 4.00(s,3H), 4.76(s,2H), 5.36(s,2H), 7.03(dd,1H,J=5.7Hz), 7.36-7.80(m,4H), 7.88-8.16(m,2H), 9.16(s,1H)

MS(m／e)；610 (M+1)$^+$

実施例62

化合物64、330mg（0.55mmol）を実施例2と同様の条件で行い、化合物65、259mg（90%）を得た。

NMR(DMSO-$d_6$) $\delta$ ：1.20(t,3H,J=7.5Hz), 2.04(dd,1H,J=5.14Hz), 2.16(s,3H), 3.20-3.70(m,3H), 3.93(s,3H), 4.63(s,2H), 5.02(s,2H), 6.32(s,1H), 7.13(dd,1H,J=5.7Hz), 7.24-8.16(m,6H), 8.57(s,1H), 9.16(s,1H)

MS(m／e)；526 (M+1)$^+$

実施例63

化合物65、239mg（0.46mmol）をTHF 8mlおよび水0.8mlに溶解し、氷冷下水素化ホウ素ナトリウム52mg（1.38mmol）を加え、同温度にて2時間攪拌した。反応溶液を飽和食塩水で

洗浄し、無水硫酸マグネシウムで乾燥後、溶媒を減圧下留去した。残渣をＴＨＦ－エーテルで粉末化し、化合物６６、１５２㎎（６６％）を得た。

NMR(DMSO-$d_6$) $\delta$ ：1.20(t,3H), 1.98(dd,1H,J=5.14Hz), 2.16(s,3H), 3.18(dd,1H,J=7.14Hz), 3.57(q,2H,J=8Hz), 3.85(m,2H), 4.64(s,2H), 5.02(s,2H), 5.14(m,1H), 5.40(s,1H), 7.00(dd,1H,J=5.7 Hz), 7.24-7.60(m,3H), 7.77(d,1H,J=8Hz), 7.92-8.16(m,2H), 8.56(s,1H), 9.17(s,1H)

MS(m／e)；４９７(M⁺)

参考例１

化合物ＫＴ5556（Ⅱａ）、２２７㎎(0.5 mmol)のエタノール２０㎖懸濁溶液に塩化チオニル１㎖を加え、加熱還流した。２時間および４時間後さらに塩化チオニルを１㎖ずつ加え、延べ８時間加熱還流した。反応混合物中の揮発性物質を減圧下に留去し、残渣をシリカゲルカラムクロマトグラフィー（クロロホルム－メタノール）により精製し、淡黄色粉末状の化合物ａ１６０㎎（６６％）を得た。

６５㎎（３４％）を得た。

融点　250～252℃（ジクロルメタン－メタノールより再結晶）

NMR(CDCl$_3$) $\delta$ ：9.42(d,1H,J=8Hz), 8.1-7.85(m,2H), 7.7-7.2(m,5H), 7.03(dd,1H,J=5,7 Hz), 5.08(s,2H), 4.05(s,3H), 3.37(dd,1H,J=7,14Hz), 3.13(s,3H), 2.21(s,3H), ca.2.20(dd,1H)

MS(m／e)；４８１(M⁺)

参考例３

化合物（Ⅱａ）、4.53ｇ（１０m mol)の無水ピリジン５０㎖溶液に、無水酢酸1.42㎖（１５m mol)を加え、室温で１時間撹拌した。反応混合物中の溶媒を減圧下に留去し、残渣に１Ｎ塩酸５０㎖を加え撹拌した。不溶物をろ取し、１Ｎ塩酸、ついで水で洗浄した。減圧下に乾燥して、淡黄色粉末状の化合物ｃ4.79ｇ（９７％）を得た。

融点　２６７～２７０℃

NMR(DMSO-$d_6$+CDCl$_3$) $\delta$ ：9.36(d,1H,J=8Hz), 8.2-7.7(m,3H), 7.7-7.25(m,4H), 7.27(dd,1H,J=5.7Hz), 5.07(S,2H), 3.98(dd,1H,J=7,14Hz), 2.35(S,3H), 2.12(dd,1H,J=5,14Hz), 1.72(S,3H)

IR(KBr) 3430,1750,1680,1640,1590,1460,1235,745 cm$^{-1}$

参考例４

化合物ｃ　2.5ｇの塩化チオニル６０㎖溶液を２時間加熱還流した。反応溶液中の塩化チオニルを減圧下に留去し、固体残渣にエチルエーテル４０㎖を加え撹拌した。不溶物をろ取し、エチルエーテルで洗浄後、減圧下に乾燥して、淡黄色粉末状の化合物ｄ　2.29ｇ（８８％）を得た。

参考例５

Ｋ－２５２、7.01ｇ（１５m mol)の無水THF１００㎖溶液を氷冷し、これに水素化リチウムアルミニウム1.14ｇ（３０m mol)を加え、室温で２時間撹拌した。メタノールを加えて過剰の還元剤を分解した後、反応混合物をセライトを通してろ過した。ろ液を１Ｎ塩酸、飽和食塩水で洗浄し、無水硫酸ナトリウムで乾燥した。溶媒を減圧下に留去した残渣をシリカゲルカラムクロマトグ

融点　193～195℃（アセトン－メタノール）

NMR(DMSO-$d_6$) $\delta$ ：9.22(d,1H,J=7.6Hz), 8.1-7.85(m,3H), 7.55-7.25(m,4H), 7.11(dd,1H,J=4.9,7.3Hz), 5.04(d,1H,J=17.7Hz), 4.98(d,1H,J=17.7Hz), 4.40(m,2H), 3.38(dd,1H,J=7.3,13.9Hz), 2.17(s,3H), 2.02(dd,1H,J=4.9,13.9Hz), 1.43(t,3H,J=7.1Hz)

MS(m／e)；４８１(M⁺)

IR(KBr) 3430,1730,1675,1635,1590,1460,745 cm$^{-1}$

参考例２

Ｋ２５２、１８４㎎（0.4 mmol）のＤＭＦ２㎖溶液を氷冷し、５０％油性水素化ナトリウム19.2㎎（0.4 mmol）を加えた。２０分後、ヨウ化メチル２５μ㎖（0.4 mmol）を加え、さらに１時間撹拌した。反応混合物にクロロホルム２０㎖を加え、この溶液を水洗後、無水硫酸ナトリウムで乾燥した。溶媒を減圧下に留去して得られた残渣をシリカゲルカラムクロマトグラフィー（クロロホルム）により精製して、淡黄色粉末状の化合物ｂ

ラフィー（クロロホルム－メタノール）で精製して、淡黄色粉末状の化合物e 5.34g（81%）を得た。

融点 266～275℃（メタノールより再結晶）

NMR(DMSO-$d_6$+CDCl$_3$) $\delta$ : 9.24 (d, 1H, J=8Hz), 8.2-7.7(m, 3H), 7.6-7.0(m, 4H), 6.74(dd, 1H, J=5, 7Hz), 4.90(d, 1H, J=18Hz), 4.69(d, 1H, J=18Hz), 4.13(d, 1H, J=11Hz), 3.91(d, 1H, J=11Hz), 3.29 (dd , 1H, J=7, 14Hz), 2.38(dd, 1H, J=5, 14Hz), 2.19 (s, 3H)

MS(m/e): 440 ($M^+$+1)

参考例6

化合物e 2.49g（5.7m mol)の無水THF 30mℓ溶液に、p－トルエンスルホニルクロリド2.70g（14.2m mol)トリエチルアミン1.97mℓ（14.2m mol)およびN,N－ジメチルアミノピリジン0.69g（5.7m mol)を加え、室温で一晩撹拌した。反応混合物にTHF 100mℓを加えた溶液を酸・アルカリ洗浄した。溶媒を減圧下に留去した残渣をシリカゲルカラムクロマトグラフィー（クロロホルム－メタノール）で精製して、淡黄色粉末状化合物f 1.11g（33%）を得た。

融点 207～210℃

NMR(DMSO-$d_6$+CDCl$_3$) $\delta$ : 9.24 (d, 1H, J=8Hz), 8.15-7.8(m, 3H), 7.65-7.2(m, 4H), 6.62(dd, 1H, J=5, 7Hz), 4.95(d, 1H, J=10Hz), 4.80(d, 1H, J=10Hz), 4.45(S, 2H), 3.05(dd, 1H, J=7, 14Hz), 2.55 (S, 3H), 2.36(dd, 1H, J=5, 14Hz), 2.12(S, 3H)

MS(m/e): 422 〔$M^+$－167 (OTs)〕

| 元素分析値 | C | H | N |
|---|---|---|---|
| 推定値（%） | 66.77 | 4.59 | 7.08 |
| 実測値（%） | 66.74 | 4.45 | 7.26 |

IR(KBr) 3430, 1670, 1640, 1595, 1460, 1175, 745cm$^{-1}$

参考例7

化合物f 594mg（1.0m mol), アジ化ナトリウム130mg（2.0m mol)のDMF 8mℓ溶液を室温で一晩撹拌した。反応混合物にTHF 50mℓを加えた溶液を酸・アルカリ洗浄した。溶媒を減圧下に留去した残渣をシリカゲルカラムクロマトグラフィー（クロロホルム－メタノール）で精製して、淡黄色粉末状の化合物g 405mg（87%）を得た。

融点 218～223℃（THF-メタノール）

NMR(DMSO-$d_6$+CDCl$_3$) $\delta$ : 9.31 (d, 1H, J=8Hz), 8.15-7.2(m, 7H), 6.87(dd, 1H, J=5.7Hz), 5.00(s, 2H), 3.99(d, 1 H, J=13Hz), 3.58(d, 1H, J=13Hz), 3.21(dd 1H, J=7, 14Hz), 2.37(dd, 1H, J=5, 14Hz), 2.19(s, 3H)

MS(m/e) : 465 ($M^+$+1)

IR(KBr) 3430, 2100, 1670, 1640, 1590, 1460, 745cm$^{-1}$

参考例8

化合物g 232mg（0.5m mol), 無水THF 7mℓ溶液に、水素化リチウムアルミニウム114mg（3.0m mol)を加え、室温で2時間撹拌した。反応混合物にTHF 30mℓを加え、セライトを通しろ過し、ろ液を酸・アルカリ洗浄した。溶媒を減圧下に留去した残渣をシリカゲルカラムクロマトグラフィー（クロロホルム－メタノール）で精製して、淡黄色粉末状の化合物h 68mg（31%）を得た。

融点 >300℃（メタノール）

NMR(DMSO-$d_6$+CDCl$_3$) $\delta$ : 9.21 (d, 1H, J=7.9Hz), 8.1-7.7(m, 3H), 7.55-7.25(m, 4H), 7.00(dd, 1H, J=5.2, 7.4Hz), 5.04(d, 1H, J=17.5Hz), 4.97 (d, 1H, J=17.5Hz), 3.25(dd, 1H, J=7.4, 13.6Hz), 3.13(d, 1H, J=12.9Hz), 2.88(d, 1H, J=12.9Hz), 2.12(s, 3H), 1.91(dd, 1H, J=5.2, 13.6Hz)

MS(m/e) : 439 ($M^+$+1)

IR(KBr) 3440, 1685, 1640, 1590, 745cm$^{-1}$

参考例9

K－252、2g（4.2mmol）をTHF 10mlに溶解し、無水酢酸4mlおよびジメチルアミノピリジン2.6gを加え室温下一晩撹拌した。反応溶液を2%塩酸水溶液、飽和食塩水溶液で順次洗浄し、無水硫酸マグネシウムで乾燥した。溶媒を減圧下留去し、残渣をシリカゲルカラムクロマトグラフィー（クロロホルム）にて精製し、化合物i、

2.12g（94%）を淡黄色粉末として得た。

NMR(CDCℓ₃) δ ; 1.76(s,3H), 2.03(dd,1H,J=5,14Hz), 2.16(s,3H), 2.56(s,3H), 3.86(dd,1H,J=7,14Hz), 3.98(s,3H), 5.07(s,2H), 6.93(dd,1H,J=5,7Hz), 7.14-7.66(m,5H), 7.80-8.00(m,2H), 9.02(d,1H,J=8Hz)

参考例10

参考例6で得られる化合物f、1700mg（2.9mmol）の無水THF50ml溶液を氷冷し、60%油性水素化ナトリウム228mg（5.8mmol）を加え、室温で2.5時間撹拌した。反応溶液を酸・アルカリ洗浄した。溶媒を減圧下に除去した残渣をシリカゲルカラムクロマトグラフィー（クロロホルム-メタノール）で精製して、淡黄色粉末状の化合物j、884mg（73%）を得た。

融点　292～296℃（分解）

NMR(DMSO-d₆) δ ; 9.31 (d,1H,J=7.5Hz), 8.1-7.75(m,3H), 7.55-7.3(m,4H), 7.22(dd, 1H,J=1.0,6.0Hz), 5.00(s,2H), 約3.35 (dd,1H), 3.29(d,1H,J=4.4Hz), 3.03(d,1H,J=4.4Hz), 2.46(s,3H), 2.00(dd,1H,J=1.0,14.7Hz)

MS(m/e) ; 421 ($M^+$)

参考例11

10%ヒドロキシプロピルセルロース溶液を化合物44、100g、乳糖40g、コーンスターチ18gおよびカルボキシメチルセルロースカルシウム10gよりなる混合物に加え、練合する。練合物を1.0mmのスクリーンを有する押出造粒機で造粒し、60℃で乾燥する。乾燥造粒物を16メッシュの篩で篩分けし、ステアリン酸マグネシウムを篩過物に添加して錠剤用顆粒を調製する。ついで常法により8mm径で1剤（170mg）あたり100mgの化合物44を含む錠剤を得る。

実験例1

代表的化合物（I）のC-キナーゼ阻害活性を、Y.Nishizuka らの方法〔J.Biol.Chem., 257, 13341 (1982)〕に準じて測定した。試験化合物の濃度を変え、酵素活性を50%阻害する化合物濃度（$IC_{50}$）を求めた。結果を第3表に示す。

第3表　合成化合物のC-キナーゼ阻害活性

| 化合物No. | $IC_{50}$, μg/ml |
|---|---|
| 3 | 0.175 |
| 4 | 0.02 |
| 22 | 0.006 |
| 24 | 0.009 |
| 25 | 0.005 |
| 35 | 0.056 |
| 46 | 0.021 |
| 47 | 0.031 |
| 49 | 0.034 |
| 50 | 0.017 |
| 57 | 0.45 |
| 61 | 9 |
| K-252（参考化合物） | 0.016 |

実験例2

代表的化合物（I）のヒスタミン遊離抑制作用を以下のようにして調べた。

体重150～180gのラットを乾エーテル麻酔下に放血致死せしめ、Sullivanらの方法〔J.Immunol., 114, 1473(1975)〕に準じて作製した肥満細胞用培養液(mast cell medium)（MCMと略記、組成：150mM NaCℓ, 3.7mM KCℓ, 3mM $Na_2HPO_4$, 3.5mM $KH_2PO_4$, 1mM $CaCℓ_2$, 5.6mMグルコース, 0.1%牛血清アルブミン, 10U/mℓヘパリン）、6mℓ/animalを腹腔内に注入した。腹部を2分間マッサージした後、開腹し腹腔内浸出液を採取した。6匹より集めた浸出液を4℃, 100×gで5分間遠心分離後、沈渣に適量の水冷MCMを加えて3回洗浄し、最終的には肥満細胞数が約3×10⁶ cells/mℓとなるように細胞浮遊液(peritoneal exudate cells, PECと略記）を調製した。なお、肥満細胞の同定は0.05%トルイジンブルーで細胞内顆粒を染色することにより行った。このようにして得たPEC 1mℓを37℃, 10分間プレインキュベートした後、種々の濃度の被検薬液0.1mℓを加えて10分間インキュベートし、フォスファチジル-L-セリン100μg/mℓおよびコンカナバリンA 1000μg/mℓそれ

それ0.1mlを加えてさらに15分間インキュベートした。氷冷した生理食塩水3mlを加えて反応を停止後、4℃、1100×gで10分間遠心分離して上清と沈渣を得た。上清および沈渣のヒスタミン量は小林の方法〔アレルギー 27, 67 (1978)〕に従い螢光法で測定した。ヒスタミン遊離率は細胞の総ヒスタミン量に対する上清のヒスタミン量の百分率として表した。また次式により被検薬液のヒスタミン遊離抑制率を算出した。

$$\text{遊離抑制率}(\%) = \left(1 - \frac{\text{薬物存在下のヒスタミン遊離} - \text{自発遊離}}{\text{薬物不存在下のヒスタミン遊離} - \text{自発遊離}}\right) \times 100$$

試験化合物の濃度を変え、ヒスタミン遊離を50%抑制する化合物濃度($IC_{50}$)を求めた。結果を第4表に示す。

第4表 代表的化合物(I)のヒスタミン遊離抑制作用

| 化合物No. | $IC_{50}$, ng/ml |
|---|---|
| 49 | 1.2 |
| 24 | 20 |
| 44 | 16 |
| 50 | 17 |

実験例3

本発明により得られた化合物の細胞生育阻害活性について以下の方法によって試験し、結果を第5表に示す。

(1) MCF7細胞生育阻害試験:

96穴マイクロタイタープレートに、10%牛胎児血清10μg/mlインシュリン$10^{-9}$Mエストラジオールを含むRPMI1640培地で$4.5\times10^{4}$個/mlに調製したMCF7細胞を0.1mlずつ各ウエルに分注する。炭酸ガスインキュベーター内で一晩37℃下培養後培養液により適宜希釈した被験サンプルを0.05mlずつ加える。72時間接触の場合には、このまま細胞を炭酸ガスインキュベーター内で細胞を培養後、培養上清を除去し、PBS(−)で一回洗浄後、新鮮な培地を0.1mlずつ各ウエルに加え炭酸ガスインキュベーター内で37℃下、72時間培養する。培養上清を除去後、0.02%ニュートラルレッドを含む培養液を0.1mlずつ各ウエルに加え37℃下、1時間炭酸ガスインキュベーター内で培養し細胞を染色する。培養上清を除去後、生理食塩水で1回洗浄し、0.001N塩酸/30%エタノールで色素を抽出後、マイクロプレートリーダーにより550nmの吸収を測定する。無処理細胞と既知濃度の薬剤で処理した細胞の吸収を比較することにより、細胞の増殖を50%阻害する薬物濃度を算出し、それを$IC_{50}$とする。

(2) $HeLaS_3$細胞生育阻害試験:

96穴マイクロタイタープレートに10%牛胎児血清2mMグルタミンを含むMEM培地で$3\times10^{4}$個/mlに調製した$HeLaS_3$細胞を0.1mlずつ各ウエルに分注する。

(1)におけるウエル分注後と同様に行う。

(3) COLO320DM細胞生育阻害試験:

96穴マイクロタイタープレートに、10%牛胎児血清100u/mlペニシリン、100μg/mlストレプトマイシンを含むRPMI 1640培地で$10^{5}$個/mlに調製したCOLO320DM細胞を0.1mlずつ各ウエルに分注する。以下(1)と同様に行い、細胞の算出はミクロセルカウンターにより行う。無処理細胞と、既知濃度の薬剤で処理した細胞の細胞数を比較することにより細胞の増殖を50%阻害する薬物濃度を算出し、それを$IC_{50}$とする。

第5表 合成化合物の細胞生育阻害活性

| 化合物番号 | $IC_{50}$(μg/ml) MCF7 | $HeLaS_3$ | COLO320DM |
|---|---|---|---|
| 3 | 0.13 | 0.01 | 0.05 |
| 4 | 0.95 | 0.07 | 0.10 |
| 24 | | 0.48 | |
| 25 | 0.84 | 0.44 | |
| 47 | 0.50 | 0.23 | 1.0 |
| 50 | | 0.28 | |

| | | | |
|---|---|---|---|
| 57 | 1.22 | 0.54 | 1.58 |
| 61 | 5.96 | 3.89 | |
| K-252 (参考化合物) | 0.51 | 0.2 | 0.27 |

発明の効果

本発明によれば化合物（I）およびその薬理的に許容される塩はC－キナーゼ阻害活性、抗ヒスタミン遊離抑制活性、血小板凝集抑制活性、抗炎症活性および細胞生育阻害活性等を有し、抗アレルギー剤、抗血栓剤、抗炎症剤および抗腫瘍剤等の活性成分として有用であると期待される。

特許出願人（102）協和醗酵工業株式会社
代表者 加藤幹夫

第1頁の続き

| ⑤1Int.Cl.⁴ | 識別記号 | 庁内整理番号 |
|---|---|---|
| // A 61 K 31/55 | ABE<br>ABF<br>ACB | |
| (C 07 D 498/18<br>207:00<br>273:00<br>307:00) | | |

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手続補正書（自発）

昭和63年2月15日

特許庁長官殿

1.事件の表示

昭和62年特許願第327858号

2.発明の名称

生理活性物質K－252の誘導体

3.補正をする者

事件との関係　特許出願人

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4.補正の対象

明細書の特許請求の範囲の欄および発明の詳細な説明の欄

5.補正の内容

(1) 特許請求の範囲を別紙の通り訂正する。

(2) 明細書第8頁13行目「800(1981)」を「800 (1978)」に訂正する。

(3) 同書第9頁2行目「を有し抗アレルギー」を「を有した抗アレルギー」に訂正する。

(4) 同書第9頁3行目「抗炎症剤にあるいは」を「抗炎症剤あるいは」に訂正する。

(5) 同書第12頁5行目「基である）」を「基であり、この内R'およびR²が水素でR³がアセチルの場合、同時にXがメトキシカルボニルでYがアセトキシではない）」に訂正する。

(6) 同書第64頁6行目、8行目および10行目「Zが」を「Xが」に訂正する。

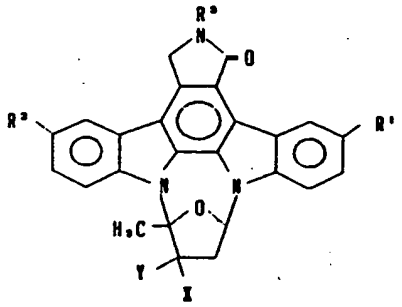
(7) 同書第77頁化合物No.9およびNo.10のR'の列「NHCOn－Pr」を「NHCOEt」に訂正する。

(8) 同書第77頁化合物No.11およびNo.12のR'の列「NHCOn－Bu」を「NHCOn－Pr」に訂正する。

(9) 同書第100頁下から5行～4行目「38.4 mg (0.8 mmol) を「9.6 mg (0.2 mmol)」に訂正する。

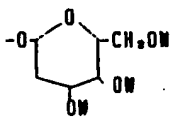
特許請求の範囲

式

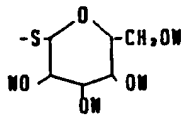


（式中、R'およびR²は同一または異なって、水素、メチル、ヒドロキシメチル、低級アルコキシメチル、低級アルキルチオメチル、低級アルキルスルフィニルメチル、ニトロ、ブロム、低級アルカノイル、ヒドロキシ、低級アルカノイロキシ、低級アルコキシ、－NR⁴R⁵（式中、R⁴およびR⁵は一方が水素で他方が水素、低級アルカノイル、カルバモイル、低級アルキルアミノカルボニルまたはフェニルアミノカルボニルであるか、両者とも低級アルキルである）、スルホン酸、-SO₂NR⁶R⁷（式中、R⁶およびR⁷は同一または異なって水素、低級アルキルまたは隣接する窒素原子と共に複素環を形成する基である）、-OCOOR⁸（式中、R⁸は低級アルキルまたは置換もしくは非置換のフェニルである）または-OCONR⁹R¹⁰（式中、R⁹およびR¹⁰は前記と同義である）を表わし、R³は水素、塩素、低級アルカノイル、カルバモイルまたは低級アルキルを表わし、Xはヒドロキシメチル、ホルミル、カルボキシル、低級アルコキシカルボニル、低級アルキルヒドラジノカルボニル、－CH＝N－R¹¹〔式中、R¹¹はヒドロキシ、カルバモイルアミノ、-NR⁹R¹⁰（式中、R⁹およびR¹⁰は前記と同義である）、グアニジノまたは2－イミダゾリルアミノである〕、－CONHR¹²（式中、R¹²はα－アミノ酸のアミノ基を除く残基であって、該アミノ酸のカルボキシル基は低級アルキルまたはベンジルでエステル化されていてもよい）、－CH₂OCOR¹³（式中、R¹³はα－アミノ酸のカルボキシル基を除く残基であって、該アミノ酸のアミノ基はベンジルオキシカルボニルまたはt－ブトキシカルボニルで保護されてい

てもよい）または$-CH_2Z$ | 式中、Zは

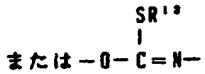



または




（式中、Wは水素、メチル、エチル、ベンジル、アセチルまたはトリフルオロアセチルである）で表わされる糖残基である | を表わし、Yはヒドロキシ、低級アルカノイロキシ、カルバモイルオキシまたは低級アルコキシを表わし、またはXとYが一体となって$-Y-X-$として$-O-C(CH_3)_2-O-CH_2-$、

または



（式中、$R'^3$は低級アルキルである）である。

ただし、Xがヒドロキシメチル、カルボキシルまたは低級アルコキシカルボニルの場合、$R^1$、$R^2$および$R^3$の内少なくとも1つは水素以外の基であり、この内$R^1$および$R^2$が水素で$R^3$がアセチルの場合、同時にXがメトキシカルボニルでYがアセトキシではない）で表わされるK-252誘導体およびその薬理的に許容される塩。